Outcome of febrile seizures: a critical review

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Submitted as partial fulfilment of the requirements for the MSc in Clinical Neurology, University of London, 2007

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2006/07

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ACKNOWLEDGEMENTS

I would like to first thank ***Prof. Simon Shorvon*** for all his help, support and advice he has given me during the course of this project. He was also my personal tutor. He has spent lot of his valuable time in supervising this project, without which I would not have completed it.

I thank ***Dr Caroline Selai*** for her support and advice during the whole course. I would also like to thank ***Daniela, Barbara*** and ***Jean***. Thanks to the library staff & my batch-mates who have helped me for the project. I thank ***Elizabeth*** who has helped me with the formatting.

I thank my parents, ***Dr. Verghese Mathew & Annie*** who has supported me in my upbringing and education. I also thank my wife ***Jilu*** and daughter ***Miriam*** for their unending support and encouragement.

I thank God for helping me and guiding me...

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ABBREVIATIONS

AAP	American Academy of Paediatrics
AED	Anti Epileptic Drug
CFS	Complex Febrile Seizure
CNS	Central Nervous System
FC	Febrile Convulsion
FS	Febrile Seizure
FSE	Febrile Status Epilepticus
HA	Hippocampal Atrophy
HS	Hippocampal Sclerosis
HVL	Hippocampal Volume Loss
ILAE	International League Against Epilepsy
MMR	Mumps Measles Rubella
MRI	Magnetic Resonance Imaging
MTS	Mesial Temporal Sclerosis
NGPSE	National General Practice Study of Epilepsy
PET	Positron Emission Tomography
PFC	Prolonged Febrile Convulsion
PFS	Prolonged Febrile Seizure
PTLE	Paradoxical Temporal Lobe Epilepsy
SE	Status Epilepticus
SFS	Simple Febrile Seizure
SUDEP	Sudden Unexpected Deaths in Epilepsy
TLE	Temporal Lobe Epilepsy

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ABSTRACT

Background: Knowledge of the outcome of febrile seizures (FS) is important for clinical practice. Reference studies of the outcome were published in the mid 1970s. Since then treatment and investigation has changed, and a review of the literature of the past 15 years can provide an insight into whether outcome has also changed.

***Aims*:** To provide a summary of published clinical data of the last 15 years, in relation to: (a) the mortality; (b) the later risk of afebrile seizure & epilepsy; and (c) the association between FS and hippocampal sclerosis (HS) /mesial temporal sclerosis (MTS).

***Methodology*:** The information for the review was extracted from a data base search of the literature in the last 15 years (01/01/1993- 30/06/2007) and from a search of cross-references in these articles.

Results: From this literature review, the following findings were derived:

(a) Mortality of FS: Simple febrile seizures (SFS) do not carry a risk of death. The risk of death associated with complex febrile seizures (CFS) is 4-13% (from 4 studies), but it is often not possible to differentiate the contribution of the underlying cause from that of the FS. The overall mortality from febrile seizures (both SFS &CFS) is very low (<1%). Febrile status epilepticus (FSE) has only a slightly higher mortality (1.6 %) than FS, and this has not apparently fallen over the past 3 decades (and this surprising finding may reflect selection bias). There is no suggestion in any of the literature that Sudden Unexpected Deaths in Epilepsy (SUDEP) occurs in association with febrile seizures, simple or complex. The longer the FSE proceeds, the worse the outcome.

(b) Risk of later afebrile seizures and epilepsy: The mean risk of later afebrile seizures is 5.8 % and 38% of the patients sustaining an afebrile seizure will later develop epilepsy. The risk of a later afebrile seizure in patients with CFS is 44 %. The risk of epilepsy after a FS increases with the duration of follow up, and has been found to lie between 2.5 % and 3.8 %

(mean risks from 23 studies). The risk of epilepsy after a CFS is 17 %. In one very large prospective study, with 23 years of follow up, the cumulative risk of epilepsy after a FS was 6.9% compared to 1.8% in controls with no history of a FS. The rate of epilepsy is higher in those with febrile seizures with onset in infancy or after the age of 3 years, then in those with febrile seizure onsets at age 1-3 years. In this study, the risk of subsequent epilepsy is also higher in those with a family history of epilepsy, cerebral palsy and low Apgar score at 5 minutes of birth. These risks do not seem to have fallen in these studies compared with studies 3 decades ago, but this may be due to differences in methodology.

(c) The Association of FS to HS/MTS: There is no evidence of any risk of HS/MTS in association with SFS. The risk of HS/MTS associated with CFS is 3 %. There is a 39 % risk of hippocampal or mesial temporal abnormalities on MRI immediately after a CFS. This high figure may be due largely to reversible, possibly oedematous, changes in the hippocampus during a prolonged febrile seizure (PFS). In serial follow up MRI studies, the risk of significant hippocampal or mesial temporal abnormalities developing after longer follow up after a CFS is 9 %. The studies of medically refractory temporal lobe epilepsy (TLE) patients show that 25 % have a history of FS (a summated mean risk from 43 studies). 44% of medically refractory TLE patients with HS/MTS have a history of FS (a summated mean risk from 35 studies). There are a number of associations reported with HS/MTS and with TLE following febrile seizures (in individual studies), including: medical intractability, good outcome following surgical therapy, post-ictal psychosis, severity and laterality of HS, and an association with the duration of the FS. Also, febrile seizures were found in several studies to more commonly result in epilepsy arising in the temporal lobe compared to other seizure locations.

1.0 INTRODUCTION

Up to 8% of all people will have at least 1 seizure during their lifetime (Hauser & Kurland, 1975). About half of these episodes are FS. FS are the most common seizures in children. It has been reported to occur in 2-4% of children (Nelson and Ellenberg, 1976; Annegers et al, 1979) but the prevalence varies. In Japan it occurs in 8 to 10% of children, and in Guam it has been reported in up to 14% of children (Shinnar & Glauser, 2002; Srinivasan et al, 2005). FS have been reported from ancient times, at least since Hippocrates, the father of modern medicine, who described it in the first century BC (Wallace, 1988).

FS usually occur between 6 months and 5 years of age and the peak incidence in the second year of life. The temperature associated with febrile illness must be greater than 38.4 degree Centigrade, although the temperature may not be evident until after the seizure episode (Shinnar and Glauser, 2002).

FS have generally been classified into SFS and CFS. A SFS is a generalised convulsive seizure without focal features, which lasts less than 15 minutes, does not recur within 24 hours and resolves spontaneously. CFS has one of the following features-lasting 15 minutes or more, associated with focal features, multiple seizures (recurrence within a 24 hour period within the same febrile illness) or has sequlae. PFS or FSE are that CFS lasting more than 30 minutes or a series of seizures during which function is not regained between seizure events in a > 30 minute period.

The outcome is the focus of this thesis. The first major modern studies of outcome were conducted in the early 1970s, and although FS were thought to have a benign outcome, it was then realised that there was a significant morbidity and mortality associated especially with FSE. The study by Aicardi and Chevrie (1970) found that there was morbidity in terms of ongoing epilepsy and neurological deficit and also mortality associated especially with FSE

in children below 3 years of age. Aicardi suggested that the duration of the status epilepticus (SE) was a critical issue and urged that the condition should be considered an emergency and therapy be initiated urgently. The introduction of benzodiazepines and also the recognition that therapy was urgent lead to an improvement in outcome. A major study was carried out in the mid 1970's by Nelson and Ellenberg (1978). This was a population based cohort study from USA and there were no deaths attributed to FS in the 1,706 FS patients studied, although 34 developed epilepsy. This has been since the major reference work in this area. However, in recent years, the issue of mortality due to epilepsy has become a focus of interest and particularly, the question of SUDEP and the therapeutic approach to FS generally has changed (notably the move to avoid long term prophylaxis). In view of this, it seems timely to review recent studies of outcome. By knowing the mortality and also the later risk of afebrile seizures and epilepsy in FS patients, the paediatric neurologist/ epileptologist will be in a better position to counsel the parents and carers. This review also attempts to address another topical issue among the neurologists, which is the association between FS and HS / MTS, which has become possible to study in recent decades because of the widespread availability of MRI scanning.

2.0 DEFINITIONS

Seizure: This is defined by the International League Against Epilepsy (ILAE) as 'a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer' (ILAE, Epilepsia 1993).

Febrile seizures: This is defined by the ILAE as a 'seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system (CNS), without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures' (ILAE, Epilepsia 1993). FS is defined by the American Academy of Pediatrics as seizure accompanied by fever without central nervous infection, and occurring in infants and children aged between 6 months and 5 years (American Academy of Paediatrics, 1996). The ILAE definition seems more appropriate as febrile seizures can occur beyond 5 years of age (Webb, 1999; Mauceri and Pavone, 2002).

Epilepsy: This is defined as a 'condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate cause. Multiple seizures occurring in a 24 hour period are considered a single event. Individuals who have only FS or only neonatal seizures are excluded from this category' (ILAE, Epilepsia 1993).

3.0 AIMS

The aims of this literature review are to determine the outcome of FS, from reports published in the past 15 years, with respect to:

1. Mortality
2. Later risk of afebrile seizures/epilepsy.
3. Association with hippocampal sclerosis/mesial temporal sclerosis

4.0 METHODS

The information for the review was extracted from data base search in the last 15 years (01/01/1993-30/06/2007). Pubmed was used as the primary database used for search, and supplemented by searches of the Embase, Cochrane and Trip databases. The reference lists of suitable publications identified from this database search were then scrutinised and publications which seemed likely to be potential sources of further data (herewith termed 'cross-references') were then also acquired and analysed. The methods used are outlined below:

4.1 Mortality from FS:

Inclusion criteria: Pubmed, Trip, Cochrane and Embase data bases were screened for articles from 1993 to 30th June, 2007 for studies pertaining to mortality from FS in the last 15 years (1993-2007).

Data analysis: The articles were analysed for the type of study, type of FS and number of deaths.

Exclusion criteria: Only articles in 'English' and pertaining to 'humans' were selected (using the 'limits' function of the databases). All studies with fewer than 5 subjects in the study were also excluded.

Yield of the search: The various searches yielded the following numbers of articles for analysis:

When the *Pubmed* was searched with the keywords 'febrile seizure' and 'mortality', there were 33 articles pertaining to the subject. When the keywords of 'febrile seizure' and 'death' were used for search we got 17 more articles. Thus there were 50 articles in total on

the subject. Of the 50 articles from Pubmed, there were 13 studies which were included in the analysis. 37 studies were excluded for the following reasons: 21 studies were not useful or relevant to the study in that they contained insufficient data for analysis in this study, 7 were review articles which did not include any data relevant to the study, 4 were single case reports, 4 were based on animal studies and 1 was an adult study.

When the *Embase* data base was used for search in the last 15 years (1993-2007), there were 11 articles when 'febrile convulsion', 'death' and 'mortality' were used as key words. 3 study articles on the subject were retrieved. Of these 3 articles, 2 were already obtained through the pubmed search. Hence there was only 1 useful article from the search. Eight articles were excluded because 3 were reviews and 5 contained no useful data.

The *Cochrane* and *Trip* database did not retrieve any new articles for the study.

Cross-references retrieved 15 articles for the review.

***Results*:** Thus, in total 29 articles suitable for the study was obtained.14 articles were from data base search and 15 were from cross- references. The studies are shown in Table 1 (Appendix A1).

4.2 Risk of later afebrile seizures and Epilepsy (recurrent afebrile seizures) in FS patients:

Inclusion criteria: Pubmed, Embase, Trip and Cochrane data bases were screened for articles from 1993 to 30th June, 2007 on the outcome of FS with regards to risk of later afebrile seizures and epilepsy (recurrent afebrile seizures).

Data analysis: The articles were analysed for the type of study, type of FS and the number of patients who developed afebrile seizures and epilepsy.

Exclusion criteria: Only articles in 'English' and pertaining to 'humans' were selected (using the 'limits' function of the databases). All studies which had less than 30 subjects were excluded.

Yield of the search: The various searches yielded the following numbers of articles for analysis:

When the *Pubmed* was searched using the keywords of 'febrile seizure' and 'epilepsy', there were 962 articles identified. With the keywords of 'febrile seizure' and 'afebrile seizure', 60 articles were identified. When the keywords of 'febrile seizure', 'afebrile seizure' and 'epilepsy' were used, 60 articles were retrieved. The articles from the two latter searches were already retrieved from the first search. Of the 962 articles from *Pubmed*, there were 30 studies which met the criteria set for the study. 935 studies were excluded for the following reasons: 724 studies were not useful or relevant to the study in that they did not contain useful data for analysis, 168 were review articles which did not include any data relevant to the study, 32 studies turned out to have less than 30 subjects, 5 were based on animal studies and 3 were adult studies.

When the *Embase* data base was used for search in the last 15 years (1993-2007), there were 896 articles when 'febrile convulsion' and 'epilepsy' were used as key words. 23 articles that met the study criteria were retrieved for analysis. Of these 23 articles, 21 were

already obtained through the pubmed search. Hence there were 2 useful articles from the search. 873 articles were excluded for the following reasons: 554 studies were not useful or relevant to the study in that they did not contain useful data for analysis, 104 were review articles which did not include any data relevant to the study, 124 were non-English articles, 45 studies turned out to have less than 30 subjects, 28 were based on animal studies, 14 were editorials and 4 were adult studies.

The *Cochrane* and *Trip* database did not retrieve any new articles for the study.

Cross-references retrieved another one article for the review.

***Results*:** Thus, in total 33 articles suitable for the study was obtained. 32 articles were from data base searches and 1 article was from cross-references. The studies are shown in Table 2 (Appendix A2).

4.3 Association of FS with HS / MTS:

Inclusion criteria: Pubmed, Embase, Cochrane and Trip data bases were screened for articles from 1993 to 30th June, 2007 on febrile seizures pertaining to HS and MTS with use of MRI.

Data analysis: The prospective studies were analysed for the type of study, the follow-up periods, number of FS patients, number of FS patients who developed hippocampal or mesial temporal abnormality and the conclusion of the study. The retrospective studies were analysed for the type of study, the number of TLE patients with HS or MTS who had antecedents of FS and the number of TLE patients who had history of FS.

Exclusion criteria: Only articles in 'English' and pertaining to 'humans' were selected in the limits for the search of articles. All prospective studies with fewer than 5 subjects have been excluded and all retrospective studies with less than 30 TLE subjects are excluded.

Yield of the search: The various searches yielded the following numbers of articles for analysis:

When the *Pubmed* was searched using the keywords of 'febrile seizure', 'mri', 'hippocampal sclerosis' and 'mesial temporal sclerosis', there were 162 articles identified. But only 52 articles met the study criteria. 110 articles were excluded for the following reasons: 58 studies were not useful or relevant to the study in that they did not contain useful data for analysis, 29 were review articles which did not include any data relevant to the study, 9 were non-English articles, 13 studies turned out to have less than 30 subjects and 1 was editorial. When the keywords 'febrile seizure' and 'magnetic resonance imaging' were used, 14 additional articles were retrieved. When the keywords of 'febrile seizure', 'magnetic resonance imaging' and 'hippocampal sclerosis' OR 'febrile seizure', 'magnetic resonance imaging' and 'mesial temporal sclerosis' were used, 3 additional articles meeting the study criteria was retrieved. Hence a total of 69 articles were retrieved from the Pubmed.

When the *Embase* data base was used for search in the last 15 years (1993-2007), there were 49 articles when 'febrile convulsion', 'magnetic resonance imaging' and 'mesial temporal sclerosis' were used as key words. Only 21 articles met the study criteria. Of these 21 articles, 20 were already obtained through the pubmed search. 28 articles were excluded for the following reasons: 7 studies were not useful or relevant to the study in that they did not contain useful data for analysis, 7 were review articles which did not include any data relevant to the study, 2 were non-English articles, 10 studies turned out to have less than 30 subjects, one article was an editorial and one was an animal-based study. When the Embase data base was searched with the keywords of 'febrile convulsion', 'magnetic resonance imaging' and 'hippocampal sclerosis', a further 10 articles meeting the study criteria was retrieved. But all these articles were already obtained through Pubmed search. Hence only one article was obtained through the Embase search.

The *Cochrane* database and *Trip* database did not retrieve any new articles that met the study criteria.

A scrutiny of cross-references yielded a further 12 articles not identified from the database searches.

Results: Thus, in total, 82 articles suitable for the study were obtained. 70 articles were from data base search and 12 were from cross- references. The studies are shown in Table 3 (Appendix A3).

5.0 RESULTS

5.1 Mortality from FS:

29 studies in the last 15 years (1993-2007) provided suitable data on the mortality associated with FS. Salient features of all 29 studies are listed in Table 4 (Appendix A4).

There were 9 prospective studies and the rest were retrospective studies. There were 8 population based studies and the rest were hospital-based studies.

Overall, there is little mortality associated with FS. In only 5 studies, were deaths recorded from FS. One of these studies referred to a death certificate study and did not provide any data on the total number of FS patients (the denominator) and so was not included in the calculation. The mortality in the other 4 studies varies from 3.5 % to 12.8 %. These 5 studies are tabulated below:

Study-Number, Author & year of publication	**Number of FS / FSE**	**Number of deaths, (%)**
1. Obi et al, 1994.	202 FS	7/202 (3.5 %)
2. Senanayake & Peiris, 1995.	Not mentioned	396 deaths in a 20 year period (1967-87)
3. Nadel et al, 1999.	39 FSE	5 (12.8%)
4. Asadi-Pooya & Poordast, 2005.	69 FSE	4 (5.8%)
5. Maegaki et al, 2005.	114 FSE	5 (4.4%)

(Key: FS = Febrile Seizure; FSE = Febrile Status Epilepticus)

There is no reported mortality from SFS in any of these studies. However, 2 studies do not distinguish between SFS and CFS: study # 1 and the study # 2 (which provides data collected from death certificates issued over a 20 year period from 1967 to 1987).The other 3 studies (studies 3, 4 and 5) do distinguish between SFS and CFS, and recorded mortality only

in association with CFS. As might be expected, the deaths were all associated with FSE. The range of mortality described in these 3 studies varies from 4.4% to 12.8 %.

The total number of patients with FS in the 28 studies was 2471 and the total reported mortality was 21.This is shown in Figure 1 (Appendix B1). Thus the overall mortality from all the studies was 0.85 % .Study by Senanayake & Peiris (1995) which used death certification was excluded for the above calculation, as it does not report the total number of FS patients. As mentioned in the previous paragraph, the actual number of deaths attributed to FS will be much lower as many of these deaths occurred in the context of acute cerebral insults.

The total number of studies providing data on FSE patients is 18. The total number of FSE patients in these studies is 876 and the total number of deaths due to FSE is 14. This is shown in Figure 2 (Appendix B2). Hence the overall mortality from FSE can be calculated to be 1.6 % on the basis of these studies. However, it should be realised that some of the children had FSE occurring in the context of acute cerebral insult and some of these deaths were more likely to have been due to underlying symptomatic cause of the status. The actual mortality from FSE therefore is probably lower. This point is elaborated upon further in the discussion section.

5.20 Risk of later afebrile seizures and epilepsy (recurrent afebrile seizures) in FS:

The total number of studies in the last 15 years (1993-2007) which describe the risk of later afebrile seizures or epilepsy (recurrent afebrile seizures) in FS patients is 33. Of these, 16 studies were prospective and the rest were retrospective. 12 studies were population based studies and the rest were hospital-based. The salient features of all 33 studies are listed in Table 5 (Appendix A5).

5.21 Risk of later afebrile seizure in FS:

Of the total 33 studies, there are 16 studies which describe the risk of a later afebrile seizure (i.e. not epilepsy). These studies (*Verity et al, 1993; Rosman et al, 1993;Pavone et al, 1993; Laditan, 1994; Nevo et al, 1995; Miyake et al, 1996; Forsgren et al, 1997;Tarkka et al, 1998; Berg et al, 1998; Pavlovic et al, 1998; El-Radhi, 1998;Webb et al , 1999; Piperidou et al, 2002;Tarkka et al, 2003;Okumara et al, 2004* and *Lee & Ong, 2004)* describe a risk of later afebrile seizures ranging from 0.25 % to 33 %. The total number of FS patients in these studies was 4160 and the number of patients who later went on to develop afebrile seizures was 241. This is shown in Figure 3 (Appendix B3). Hence the summated risk of later afebrile seizures in FS in these studies is 5.8 %.

It is interesting to note that 50 of the patients in 6 of the above 16 studies were followed up (*Forsgren et al, 1997; Berg et al, 1998; Pavlovic et al, 1998; El-Radhi, 1998; Piperidou et al, 2002* and *Lee & Ong, 2004*), 19 developed epilepsy; i.e., 38 % developed epilepsy if they had history of febrile seizures that lead to an afebrile seizure.

There are 2 studies which describe the risk of a later afebrile seizure in CFS patients. The studies report a rate of 44% of CFS patients developing later afebrile seizure. The studies are tabulated below:

Study-Number, Author & year of publication	**Number of CFS patients**	**Afebrile seizure- Number; (%)**
1.Pavone et al,1993	68	30/68; (44 %)
2.Laditan,1994	43	19/43; (44 %)

(Key: CFS-Complex Febrile Seizure)

The total number of CFS patients in these 2 studies was 111 and 49 developed afebrile seizure. Hence 44 % developed afebrile seizures in these two studies overall, where the follow up ranged from 3-5 years. Both these studies were retrospective in nature.

5.22 Risk of later epilepsy in FS:

Of the total 33 studies there are 23 studies which describe the risk of epilepsy in FS patients (*Tsai & Hung, 1995; VanEsch et al,1996; Knudsen et al, 1996; Forsgren et al, 1997; Hackett et al, 1997; Berg et al, 1998; Pavlovic et al,1998; El-Radhi, 1998; MacDonald et al,1999; Sapir et al, 2000; Chang et al, 2000; Piperidou et al, 2002; Kjeldsen et al, 2002; Mauceri & Pavone, 2002; Borusiak & Herbold, 2003; Metsäranta et al, 2004; Yücel et al, 2004; Vestergaard et al, 2004, Lee et al, 2004; Birca et al, 2005; Yu et al, 2007; Hussain et al, 2007* and *Vestergaard et al, 2007*). Of these, 12 were prospective studies. 10 were population based studies and the rest hospital-based. The hospital-based studies report 0.1 % to 32 % risk of epilepsy in FS patients. The higher figure and the wider range noted in the hospital-based studies could be due to selection bias of the patients, as more serious FS are admitted. The population based studies report a figure of 2 to 6 %. It is interesting to note that estimate of the risk of later epilepsy depends on the years of follow-up in most of the studies. Studies with a follow-up of under 10 years show a figure of around 2 to 4 % risk, but studies

with longer follow ups (>10 years) show a higher risk of 4.5 % to 7.5 %. The total number of FS patients in the studies was 21,901 and of these 544 developed epilepsy during the follow up. Thus, overall, 2.5 % of FS patients developed epilepsy. The studies with follow-up of more than 20 years (*Kjeldsen et al, 2002; Mauceri & Pavone, 2002* and *Vestergaard et al, 2007*) were not included in the above calculation of the risk because it had a very long follow up period. The long follow up could misinterpret the risk figure because other causes for epilepsy could also be involved. If these studies are also included, the total number of FS patients will be 72616 and the number of patients who developed epilepsy will be 2754. This is shown in Figure 4 & 5 (Appendix B4 & B5). Thus the summated mean risk of epilepsy in FS from all the studies is 3.8 %.

There are 5 studies which describe CFS leading to epilepsy. This is shown in Figure 6 (Appendix B6). These studies report a 2.1 % to 32.1 % risk of later epilepsy in CFS patients. The total number of CFS patients included in these studies is 427, of whom 73 developed epilepsy; i.e., a summated rate of 17.1 %. These studies are tabulated below:

Study- Number, Author, Year	**Number of CFS patients**	**Epilepsy- Number ;(%)**
1.Van Esch, 1996	57	3; (5.3 %)
2.Sapir, 2000	48	13; (27.1 %)
3.Metsäranta, 2004	116	5; (4.3 %)
4.Yücel, 2004	159	51; (32.1 %)
5.Hussain, 2007	47	1; (2.1 %)

(Key: CFS- Complex Febrile Seizure)

5.30 Association of FS with HS/MTS:

82 studies in the last 15 years (1993-2007) provided suitable data on the association between FS and HS/MTS. Salient features of all 82 studies are listed in Tables 6.11, 6.12, 6.21 and 6.22 (Appendix A6,A7, A8 and A9).

There are no studies in the last 15 years which report SFS followed by hippocampal or mesial temporal abnormalities. But there are studies which report CFS leading to hippocampal or mesial temporal abnormalities.

5.31 FS leading to Hippocampal / Mesial temporal abnormality on MRI immediately after the seizure episode:

There are 5 studies in the last 15 years (*VanLandingham et al, 1998; Szabó et al, 1999; Grünewald et al, 2001; Scott et al, 2002* and *Natsume et al, 2007*) which reported the results of MRI scanning of the mesial temporal areas carried out on a single occasion in the immediate aftermath of the CFS. The salient features of the 5 studies are mentioned in Table-6.11 (Appendix 6). These five studies report that 9.5 % to 100 % of CFS patients showed hippocampal or mesial temporal abnormalities immediately after the seizure episode. The overall number of CFS patients in these studies is 78, of who 30 exhibited hippocampal or mesial temporal abnormalities in association with the history of CFS. Thus the studies showed that the mean risk of hippocampal or mesial temporal lobe abnormalities is 38.5% immediately after a CFS. The abnormalities reported were increased hippocampal volumes and the hippocampal asymmetry between the two sides. It is interesting to note that 83.3 % of CFS patients who developed abnormalities on neuroimaging after the seizure episode had FSE.

5.32 Hippocampal / mesial temporal lobe abnormality followed up with MRI study:

There are 4 studies (*Tarkka et al, 2003; Scott et al, 2003; Scott et al, 2006* and *Farrow et al, 2006*) which prospectively looked at the progression of hippocampal/mesial temporal abnormalities using serial MRI scanning. The salient features of the 4 studies are mentioned in Table-6.12 (Appendix 8).

The studies had a follow-up period ranging between 4 months and 12 years. The studies report a figure between 0% and 36 % of CFS patients developing significant hippocampal/mesial temporal abnormality in the follow up period. The overall number of patients in these studies was 77 and 7 developed significant abnormalities. Thus a mean of 9 % of patients developed significant hippocampal/mesial temporal abnormality on follow-up. But only 2 of 77 patients were reported to have HS (HS was said to be present radiologically, if there was a smaller hippocampi accompanied with longer T2 relaxation times). Thus only 2.6 % of CFS patients followed up for between 4 months and 12 years developed HS. It is interesting to note that the prospective study (*Tarkka et al, 2003*) with the maximum number of patients and the longest follow up had no cases developing either HS or MTS even after 12 years of follow up. It is therefore not possible to come to a clear conclusion regarding the risk of HS developing after CFS, especially PFS. Most of the studies had very few subjects, and the prospective study with the greatest number showed the lowest figure. However, it is clear from all these studies that the risk of HS or MTS being found in association with a CFS is low.

5.33 History of FS in TLE patients with HS/MTS with MRI study:

There are 35 studies in the past 15 years (1993-2007) which looked at the history of febrile seizures in TLE patients with either HS or MTS. The salient features of all 35 studies are listed in Table-6.21 (Appendix 9)

As expected all these studies were from hospitals and were done in tertiary neurosurgical units as part of the pre-surgical evaluation for temporal lobectomy. Most of the patients in these studies were refractory to medical treatment of TLE and hence referred for lesional surgery.

The studies report 16 % to 74 % of TLE patients with either HS or MTS had a past history of FS. The total number of TLE patients with either HS or MTS on MRI in these studies was 3268 and 1425 had a past history of FS. This is shown in Figure 7 (Appendix B7). Hence, by summating the figures from these studies, a mean of 43.6 % of TLE patients with either HS or MTS on MRI had past history of FS.

5.34 History of FS in TLE patients with MRI study:

There are 43 studies in the past 15 years (1993-2007) which looked at the history of febrile seizures in TLE patients. The salient features of all 43 studies are listed in Table-6.22 (Appendix 9).

All the studies were hospital-based except one. The studies report 3 % to 56 % of TLE patients had a past history of FS. The total number of TLE patients in these studies was 5542 and 1384 had a past history of FS. This is shown in Figure 8 (Appendix B8). Hence, by summating the figures from these studies, a mean of 25 % of TLE patients had a past history of FS.

6.0 DISCUSSION

6.1 Mortality from FS:

The study from the mid 1970's by Nelson and Ellenberg (1978) is usually considered as the 'reference' study which forms the basis for the current opinion regarding the outcome on FS and its mortality. This was a population based cohort study from USA and there was no deaths attributed to FS in the 1,706 FS patients studied, although 34 developed epilepsy. Since then, the approach to treatment has changed and investigational methods have improved especially the introduction of MRI scanning. Furthermore, in adult epilepsy, it has become clear that SUDEP occurs in a small but significant number of patients. In this thesis, I have reviewed the more recent literature (that published over the past 15 years) to see whether our views of outcome should be adjusted.

6.11 Mortality from SFS:

None of the studies reviewed reported any mortality associated with SFS. In the past, it seems likely that any mortality reported was due to the traditional methods of treatment especially in the developing world.

I here highlight some of the important studies. The NGPSE (National General Practice Study of Epilepsy) study looked at the neurological sequlae after a follow-up of around 12 years of 220 children with FS. In this prospective study (Cockerell et al, 1994), the authors found that none of the patients followed-up died. The Australian retrospective study (Rainbow et al, 2002) found no mortality in the 46 FS patients studied. The Italian study (Verrotti et al, 2004) which prospectively looked at the effectiveness of intermittent oral diazepam prophylaxis in FC in 110 patients found that none of the patients died in the 4 year

follow-up period. The Virginia study (Shinnar et al, 2001) looked prospectively and found no deaths in either the FSE or FS group studied over 10 years. In none of these studies, was SUDEP suggested to account for any deaths.

6.12 Mortality from CFS:

A small mortality is recorded from CFS in the last 15 years and especially in those with FSE (FS lasting beyond 30 minutes with no gain of consciousness in between). It is interesting to contrast these findings with the earlier studies (particularly of Aicardi). The study by Aicardi and Chevrie (1970) on convulsive SE in infants and children showed that FSE was associated with bad outcome especially in younger children (< 3 years).The study found 11 % mortality associated with status and half of this was attributed to the seizure and the rest due to causative cerebral disease. It is interesting to note that the definition for status was duration more than 1 hour. Later studies, including the National Institute of Neurological Disorders and Stroke (NINDS) Collaborative Perinatal Project (Nelson and Ellenberg, 1978) reported a much better outcome. The change was probably due to two main factors: Firstly, treatment with benzodiazepines became widespread and was started earlier and with a greater sense of urgency than in the pre-Aicardi days. Secondly, more aggressive treatments and protocols came into use in the paediatric ICUs for the management of FSE like barbiturate anaesthesia. It seems for my review of the most recent studies, that this improved outcome has been maintained – in spite of the fact that prophylactic therapy after a first FS is no longer widely used. Another recent development has been the greater use of 'pre-hospital' therapy which is likely to have reduced the number of PFC.

Here, I consider some of the findings in more detail. The study from Benin, Nigeria (Obi et al, 1994) reported 7 deaths in 202 FS (3.4 %) patients. This was a hospital-based prospective study and the deaths were due to aspiration pneumonia in 5 cases and 2 were due

to tetanus with measles. Of the 5 deaths due to aspiration pneumonia, 2 of the patients had malaria and 3 had upper respiratory tract infection. This emphasises one of the main problems in studying outcome – and that is to disentangle the effects of the febrile seizure from that of the underlying condition. In this study, for instance, the authors do not specify whether the patients had cerebral malaria or measles encephalopathy. The number of deaths, if these patients were excluded, is only 3 deaths (1.5 %). The study from St Mary's hospital, London (Nadel et al, 1999) showed that 5 out of 39 patients with acute febrile encephalopathy died. Three had bacterial meningitis, one had a metabolic disease and the other intra-ventricular haemorrhage. In this retrospective study, the underlying condition seems itself more likely to have resulted in death than the FS. Another study which showed mortality associated with FSE is the Iranian study (Asadi-Pooya and Poordast, 2005). This retrospective study shows that 4 of the 69 patients admitted with PFS died. The morbidity and mortality figures in this study are at the higher end of range than usually reported. Another recent retrospective hospital-based study from Japan (Maegaki et al, 2005) reported a mortality of 5 among 114 FSE patients. The authors also concluded from the study that seizure duration of more than 2 hours is associated with poorer outcome.

The study from Sri Lanka (Senanayake and Peiris, 1995) used death certification to identify mortality related to convulsive disorders. The study was of death certificates issued in the Kandy district over a period of 20 years (1967-1987).The study found that around 45% of total deaths due to convulsions were due to FS. It would have been interesting if the authors could have given information regarding the prevalence of FS in the area and the figure of 396 deaths is surprisingly high. The study does not reveal if any of the children suffered from CNS infections or other acute cerebral insult. Interestingly, the authors mention that most deaths occurred in peripheral regions, and it can be speculated that in many there was a marked delay in treatment. It is interesting that this study spanned the period when treatment

of FS changed (more urgent therapy and the widespread use of benzodiazepines). The authors report that the rates of death fell in successive decades - from 37/1000 to 9.5/1000 in the 20 year period. This trend was also noticed with FS. In none of these studies, was SUDEP suggested to account for any deaths.

I here highlight some of the important studies which looked into mortality associated with FSE and found no mortality. The Child Health and Education Study (Verity et al, 1993) is another large population based cohort study conducted in the UK – of 398 children with FS. There were no deaths reported, from prolonged (>15 min) or even lengthy (>30 min) FS (i.e., FSE). The study from Finland (Metsäranta et al, 2004), a hospital-based retrospective showed no mortality in 116 FSE patients. The Rotterdam study (van Esch et al, 1996) was a hospital-based study which retrospectively looked at the neurological outcome of 57 FSE patients and none of the patients died. The Okayama study (Nishiyama et al, 2007) was a recent retrospective study and none of the patients with FSE died. The Liverpool study (Hussain et al, 2007) was a 5 year retrospective hospital-based study which showed no mortality in the 47 PFS patients. An Israeli study (Lahat et al, 2000) comparing intranasal midazolam with intravenous diazepam for treating PFS showed no mortality in the 47 patients studied. A similar conclusion was obtained form the North London Status Epilepticus in childhood Surveillance Study (NLSTEPSS), which showed no mortality in the 56 PFS patients (Chin et al, 2006).

In summary, it appears that the risk of death due to FS is low and the only significant mortality is associated with complex or prolonged seizures, but even here most of the deaths can be attributed primarily to the underlying cause of the FS or FSE rather than to the seizure itself. FS do not seem to carry a risk of SUDEP. What is also clear is that the longer FSE proceeds, the worse are the outcome.

6.2 Risk of later afebrile seizures and epilepsy in FS patients:

There are two large studies in the 1970's which has formed the foundation for the present view on the outcome of FS with regards to later risk of epilepsy. The first study (van den Berg and Yerushalmy, 1969) found that the risk of later epilepsy to be around 3% and the second study was the National Institute of Neurological Disorders and Stroke (NINDS) Collaborative Perinatal Project (Nelson and Ellenberg, 1978) which reported a 2% risk of later epilepsy in FS patients. The first study was performed at a time when the emergency use of early benzodiazepine therapy was not widespread. These studies concluded that the risk of later development of epilepsy in FS patients is low but slightly higher than the general population. This conclusion is largely confirmed by my review of the more recent literature, although generally somewhat higher rates were reported.

I here present some of the important studies related to the risk for later development of afebrile seizures and epilepsy. The Boston study (Rosman et al, 1993) was a prospective study, where 406 children with FS were evaluated for the effectiveness of diazepam administered during febrile illness to prevent recurrences of FS. When these patients were followed up over 1.9 years, 0.3 % developed afebrile seizures. The prospective hospital-based study conducted in USA (Berg and Shinnar, 1996) showed that 6% of CFS patients developed afebrile seizures and 0.7 % developed epilepsy when they were followed up for 2 ½ years.

The Nagoya study (Okumara et al, 2004) was a hospital-based retrospective study that suggested that the daily or intermittent prophylactic treatment in FS patients will not reduce the risk of later development of afebrile seizures, as 2 out of the total of 43 patients who developed unprovoked seizures were on daily antiepileptic drugs. It is difficult to accept this conclusion unreservedly, as the sample size was small, follow-up period was short and that it was a hospital-based study creating bias towards inclusion of atypical patients.

The Finnish prospective study of Tarkka et al (1998) was a hospital-based study of the outcome of the first FS. The authors found that only 1 % FS patients developed afebrile seizure with a follow-up of 2 years. The same group (Tarkka et al, 2003) later reported 2 % FS patients developed afebrile seizure with a longer follow-up of 8-15 years.

The NGPSE study by MacDonald (1999) was a prospective community based study followed-up for 11 years and found that 6 % of FS patients developed epilepsy. The Montreal group (Birca et al, 2005) retrospectively studied the influence of family history on the presentation and outcome of FS. Of 482 children with FS, 37 developed epilepsy (8%). 11 of the patients had TLE by EEG (there was no neuroimaging data). The higher proportion of epilepsy could be due to the fact that it was a hospital-based study with selection bias and also due to the fact that there was a large drop out from the original 1104 FS patients.

The Glostrup study from Denmark (Knudsen et al, 2000) looked at the outcome of FS in a hospital-based retrospective study; he found that 6 of the 272 children with FS developed epilepsy. A Greek community based retrospective study (Piperidou et al, 2002) looked at the outcome of FS by a retrospective questionnaire given to parents of adolescents. The authors found that 2 of the 56 patients developed afebrile seizures and another 2 developed epilepsy. The study missed patients who dropped out of secondary school and also those who may not have replied to the questionnaire. In a Serbian epidemiological study (Pavlovic et al, 1999) of 154 FS patients, 5% developed epilepsy. The prospective population based study had a follow-up of 5 years from their first FS.

There are reports of the outcome of FS occurring after the age of 5 years ('late febrile seizures'). A retrospective hospital-based study (Webb et al, 1999) showed that 10% of patients with late FS developed afebrile seizures, at a follow up of 5 years.

A retrospective study from Italy (Mauceri and Pavone, 2002) reported that 5.5 % of FS patients developed epilepsy. This study has some drawbacks in that it was calculated from the hospital records and only a quarter of the patients from were used for the study because of 'lack of information'. A Danish population based twin study (Kjeldsen et al, 2002) looked at the genetic and environmental factors related to FS. The study found a lifetime prevalence of FS in 2.8 % and 7.5 % of FS patients developed epilepsy with a follow-up between 12 and 40 years.

A population based prospective study (Vestergaard et al, 2004) of all children born in Denmark between 1991 and 1998 showed that out of 17,986 FS patients, 355 (2%) patients developed epilepsy when they were followed up for 8 years. The study looked at the susceptibility to FS when they were given MMR vaccination. The authors found that there is increased risk of recurrent FS but no increased risk of epilepsy with MMR. This was followed by a large prospective study (Vestergaard et al, 2007) in a population based cohort of 1.54 million persons born in Denmark between 1978 and 2002. This study gives valuable information especially with regards to risk of epilepsy in FS patients. Only 13% of epilepsy patients had prior history of FS. After 23 years of follow-up of FS patients, the overall cumulative incidence of epilepsy was 6.9 % with respect to only 1.8 % for those without history of FS. The association between FS and epilepsy was found to be modified by time since the first FS. The rate of epilepsy was 26 times higher during the first 3 months after the onset of FS but it reduced to a 3 fold higher rate after 8 years of FS onset. The children who had FS onset in infancy or after 3 years of age had a higher rate of epilepsy within the 2 years after the first seizure with respect to those who developed FS between the ages of one and three. The study also revealed that there was a higher risk of epilepsy in those with a family history of epilepsy, cerebral palsy and low Apgar score at 5 minutes of birth.

A hospital-based retrospective study from Tel Aviv (Sapir et al, 2000) noted that 27% of CFS patients developed epilepsy. In a Rotterdam hospital-based study amongst FSE patients (van Esch et al, 1996), 5 % developed epilepsy over a 22 month follow-up. A hospital-based retrospective study (Metsäranta et al, 2006) from Tampere, Finland found 4 % of FSE patients developed epilepsy. The Istanbul hospital-based retrospective study (Yücel et al, 2004) looked at the prognosis of children with CFS. The authors found that 51 out of the 159 (32%) CFS patients developed epilepsy – a very high rate indeed. Their definition of CFS was however different from that in other studies and included patients with neonatal seizures.

What can we conclude from these studies? It is clear that there is a slightly increased risk of later epilepsy in children who experience FS, especially CFS. The rate has not fallen since the time of the NINDS Collaborative Perinatal Project (Nelson and Ellenberg, 1978), and indeed in general higher rates are reported. This is in spite of generally improved therapy of FS (earlier intervention, out of hospital intervention and widespread use of benzodiazepines). The rate of epilepsy seems usually to be between 4-7%, and conversely the number of patients with epilepsy and a history of FS is 13% (a figure from the large-scale Danish study of Vestergaard and colleagues (2007). Although these figures are somewhat higher than equivalent figures from the NINDS study, it is not possible to conclude that the rates have actually worsened. The recent studies have differences in methodology, improved ascertainment, better records systems and so on and these technical differences could easily explain the apparent difference in the findings. Another possibility is that the better early therapy of FS has reduced the number of seizures evolving into FSE and thus the cases of FSE now occurring are generally more severe than previously. This may explain the paradox of improvement of therapy and apparently worsened outcome of FSE. Without knowing the proportion of cases of FS evolving to FSE, it is not possible to confirm this point.

6.30 Association between FS and HS / MTS:

The nature of the association between FS and HS/MTS remains one of the most controversial issues in paediatric neurology. An important element of this controversy revolves around the question as to whether FS cause HS or whether the HS is the cause of the FS. My review can not illuminate this point. What I have done here is largely to collect the data on the frequency of the association, and this does not imply any causality. However, the few small serial MRI series (discussed below) do show in my opinion that – at least in some (possibly a minority of) cases – HS is not present at the time of the FS but develops subsequently. If the causative link between them is established, it will help in developing preventive measures for the development of HS/MTS.

6.311 Febrile seizures leading to hippocampal / mesial temporal abnormality on MRI:

A prospective hospital-based study from Durham (VanLandingham et al, 1998) showed that 4 of the 27 CFS patients who had MRI soon after the CFS which were prolonged and focal in nature showed increased hippocampal volume and T2 intensity, and 2 of them later developed hippocampal atrophy. The authors concluded that the CFS produced acute hippocampal injury. Another study from Cleveland (Szabó et al, 1999) showed smaller hippocampal volumes and larger right to left hippocampal volume ratios in 5 of the patients with CFS studied in the acute phase - and one of them had significant hippocampal asymmetry. The authors concluded that they could not distinguish between the possibility that the hippocampal asymmetries reflected a pre-existing developmental abnormality, or that the hippocampus was damaged during the CFS, or finally that this was a normal age related change. A study from Sheffield (Grünewald et al, 2001) showed hippocampal asymmetry in the acute phase of 10 of the 13 CFS patients. They found that hippocampal volume ratio was greater in the febrile seizure group with respect to controls and afebrile seizures. Another

study from London (Scott et al, 2001) tried to look at whether quantitative MR techniques could be used to distinguish MTS in patients with a history of PFS and those without it. The study revealed that CFS patients had smaller hippocampi and longer T2 relaxation time with respect to the controls. These patients also had hippocampal asymmetry with respect to both volume and T2 relaxation times. This suggested that PFS may be one of the pathways that lead later to MTS. Another study by the same group (Scott et al, 2002) of 21 children with CFS showed that PFC was associated with larger hippocampal volumes and which were not seen with afebrile SE. The authors also noted that T2 relaxation times were highest in the first 2 days after the PFC and was not elevated after day 3 of PFC. This suggested that the abnormalities could be due to hippocampal oedema, caused by the PFC, and which resolved subsequently. A study from Nagoya (Natsume et al, 2007) showed that hippocampal volumes were larger in refractory PFS of more than 60 minutes duration. It also showed that these patients had hippocampal hyperintensity on diffusion-weighted imaging (DWI).Although the study was of only 12 patients, it suggests that refractory PFS of more than 60 minutes cause structural changes in the limbic structures.

6.312 Hippocampal / mesial temporal lobe abnormality followed up with MRI:

There are prospective studies in which serial MRI imaging has shown changes over time in hippocampus and mesial temporal structures after CFS. These studies provide the best evidence of progressive change. The study of Scott and colleagues (2003) of 14 patients (these were the same patient group included in the earlier cross-sectional study; Scott, 2002) was carried out with follow-up MRI repeated 4-8 months after the complex febrile seizure. 5 patients developed hippocampal asymmetry outside the 95^{th} percentile but none had T2 relaxation abnormality consistent with the radiological criteria of MTS. One explanation was that the re-imaging was carried out at too short a time interval and the patients were in the lag

phase of development of MTS. Conversely, another study done by the same group (Scott et al, 2006), showed that the apparent diffusion co-efficient (ADC) of patients whose imaging were done within 2 days of PFC, reduced in comparison to those whose initial imaging was done between days 3 to 5 after the PFC when studied with a follow-up imaging done 5 months later. It also evolved that there was no age dependent decrease in ADC of hippocampus over time in those patients with PFC with respect to controls. The authors suggested that the changes could reflect a developmental abnormality rather than consequential damage due to the PFC.

Conversely, the hospital-based prospective study from Sheffield (Farrow et al, 2006) raises the possibility that PFC is more malignant than previously thought. They found that 2 of the 8 patients that were followed up developed HS over a mean of 6.5 years. The authors suggested that if the initial imaging after a PFC was associated with hippocampal asymmetry it is very likely that it may lead to HS.

One study from Finland refutes the link between a PFC and MTS. The study (Tarkka et al, 2003) followed-up 32 FS cases, especially those with a PFC or those who developed unprovoked seizure after their first FS, with the logic that they maybe at higher risk of developing MTS. The study showed that none of the high risk FS patients developed MTS. The duration of the PFS was between 45 and 95 minutes, though the majority had below 60 minutes. One explanation is that PFS of less than 60 minutes are unlikely to lead to MTS, whereas longer convulsions are more dangerous.

6.32 History of FS in TLE patients with HS /MTS:

It is possible to look at the association from the opposite perspective, and a number of studies from different groups have reported findings in the past 15 years.

I here highlight some of the important studies. The first was a hospital-based study from the Institute of Neurology in London (Kuks et al, 1993), in which 36% of patients with drug resistant partial epilepsy with HS identified by MRI were found to have a history of childhood FS. The hippocampal volume loss was associated with past history of FS, and there was also a significant association with a diffused pattern of hippocampal volume loss. The patients with hippocampal volume loss without past FS often had a focal pattern. A study from Memphis, USA (Davies et al, 1996) reported 32% of TLE patients with HS had history of FS. The study found a positive correlation between the presence of severe HS and a history of FS. A hospital-based retrospective study from China (Xiao et al, 2004) found that one third of the TLE patients with HS had history of FS. The authors noted that a FS was the second most common antecedent (after trauma) in HS patients. A study from New Haven, USA (Aaron et al, 2005) noted that 34 % of TLE patients with MTS had a history of FS. The study found that TLE without abnormality on MRI study or histopathology had a lower chance of a past history of FS in comparison to the classical TLE with MTS. A similar conclusion was seen in a study from Italy (Labate et al, 2006).

A study from the Institute of Neurology, the Institute of Child Health and Great Ormond Street Hospital for Children, London (Van Paesschen et al, 1997a) found 44% of TLE patients with HS had a history of FS. A history of FS was associated with unilateral HS but not with bilateral HS. Another cohort of patients were studied by the same group (Van Paesschen et al, 1997b) in which 62% of TLE patients with HS were found to have a history of FS. The study also showed that hippocampal atrophy in HS was associated with neuronal cell depletion and gliosis. A study from Alabama, USA (Kuzniecky et al, 1996) also reported that 55 % of TLE patients with MTS had a history of MTS. The authors found variable patterns of atrophy in the hippocampus in association with CFS. A study from UK (Thom et

al, 2002) reported that severity of granule cell disorganization correlated with severity of hippocampal neuronal loss but does not depend on antecedents like FS.

Other aspects of the association of FS to HS have been investigated. A study Melbourne Australia (Bower et al, 2000) reported 48% of TLE patients with HS had history of FS. The investigation was conducted to see whether FS were particularly associated with severe HS, but no association was found. In this study, the authors concluded that HS may be a pre-existing abnormality. A study from Glasgow (Stephen et al, 2001) found that 37% of partial epilepsy patients with MTS had history of FS, and that the MTS related epilepsies responded poorly to AED when compared with other brain pathologies. Another study from Seoul (Kim et al, 1999) reported that TLE patients with MTS who had a history of FS responded poorly to AEDs especially with EEG changes. Conversely, a hospital-based prospective study (Hardy et al, 2003) from Washington, USA found 25% of TLE patients with MTS had a history of FS and found that only a past history of SE predicted a poorer outcome. A hospital-based study from Melbourne (Briellmann et al, 2001) tried to find the characteristics of seizures in families of TLE patients with HS. The study found that 65 % of TLE patients with HS had history of FS. The study found that a family history of FS maybe a risk factor for TLE with HS, and proposed that genes played a role in the pathogenesis of HS. A hospital-based retrospective study from Budapest (Janszky et al, 2003c) reported that 47 % of TLE patients with HS had history of FS and noted that right HS was more common than the left in FS patients. Another study by the same group (Janszky et al, 2003a) found that bilateral interictal discharges in TLE patients were associated with earlier onset of epilepsy. In a study from Kyoto, Japan (Kanemoto et al, 1996), unilateral HS patients were often associated with a past history of CFS. They also found episodes of psychosis, especially postictal psychosis, were more common in patients with unilateral HS.

The outcome of temporal lobe surgery has also been correlated to the presence of FS. A third study by the group from Budapest (Janszky et al, 2003b) found that TLE patients with HS who had a history of FS had a better post-surgical outcome than those with out. A hospital-based study from Birmingham Alabama (Burneo et al, 2005) reported that 38 % of TLE patients with MTS had a history of FS and found that African-Americans had a poorer post-surgical outcome. However, a subsequent study by the same group (2006) came to the opposite conclusion. In this study of larger numbers of patients, 70 % of the TLE patients with MTS had a history of FS and race did not influence post-surgical outcome.

Although the hippocampus has been usually the focus of study, one study from Seoul, South Korea (Choi et al, 1999) assessed white-matter changes in the temporal lobe of MTS patients. The study reported 36% of TLE patients with MTS had history of FS. White- matter changes was noted in 32% of the patients. Histopathology of the specimens showed larger number of heterotopic neurons in patients with frequent history of FS. A hospital-based study from Paris (Thivard et al, 2005) also noted that diffusion abnormalities on MRI were not restricted to the pathologic hippocampus.

6.33 History of FS in patients with TLE:

I here highlight some of the important studies which looked at the history of FS in TLE patients. A hospital-based study from Kyoto (Kanemoto et al, 1996) showed that 32% of non –lesional TLE patients had history of CFS, which is less than the 51% of TLE patients who had HS. They also found that HS was associated with past history of FS. The study by the same centre (Kanemoto et al, 1998), showed a close association between CFS and TLE. The study noted that TLE patients with past history of CFS had earlier onset of seizures, presence of autonomic auras and a higher imaging evidence of unilateral MTS. The retrospective hospital-based study from Montreal (Cendes et al, 1993) found that PFS were

associated with more severe MTS. Another hospital-based retrospective study from Rochester (Trenerry et al, 1993) reported 41% of TLE patients had history of FS in childhood and found that HA was associated with earlier onset of recurrent seizures especially in left TLE patients. A hospital-based retrospective study from (Hufnagel et al, 1994) found that TLE patients with bilateral epileptiform discharges performed badly after surgical treatment.

A study from Japan (Kodama et al, 1995) reported that 24% of TLE patients admitted in their psychiatry department had past history of FS, and in particular CFS. A hospital-based study from Brazil (Alessio et al, 2004) documented memory deficits was associated with hippocampal atrophy.

A hospital study from Melbourne (Harvey et al, 1995) reported that 39 % of TLE patients had history of FS in childhood. They found that 57% of TLE patients had HS and around 50% of patients were younger than 10 years of age. The authors suggested that HS may be under diagnosed in children and may be the cause for TLE rather than a consequence of TLE. Another hospital-based study from New York (Barr et al, 1997) found that hippocampus was smaller on the side of the seizure focus. A hospital-based study from Sydney (Lawson et al, 2000) found that CFS was associated with smaller hippocampal volumes than SFS.

A hospital-based study from Finland (Salmenperä et al, 2001) found that 6% of TLE patients had history of FS. The authors noted that CFS was associated with hippocampal volume loss. Other factors which could cause hippocampal volume loss were early onset of seizures and frequent seizures.

A hospital-based study from Nashville (Hamati-Haddad and Abou-Khalil, 1998) found that 25% of TLE patients had history of FS. They found that there is a slight preference for the temporal lobe involvement in those with past history of FS and the prolonged duration of the seizure was the most common feature in TLE patients. A hospital-based study from

Milan (Chabardés et al, 2005) noted that temporal pole involvement is common in the initiation of TLE seizures. A hospital-based study from Memphis, USA (Davies et al, 1999) noted that 40 % of patients with TLE had a past history of FS. They also noted that left HS is more common with past history of FS.

A hospital-based retrospective study from Montreal (Guerreiro et al, 1999) tried to correlate the different patterns of hippocampal and amygdalar abnormalities. The authors found that hippocampal atrophy was associated with earlier seizures, antecedent FS and memory deficits. Another study from Liverpool (Keller et al, 2002) tried to look at the grey matter abnormalities in medically refractory TLE. The authors suggested that early antecedent's like FS could be the cause for HS.

A large hospital-based retrospective study from Nashville, USA (Abou-Khalil et al, 2007) found that 24 % of TLE patients had history of FS. The authors pointed out that the susceptibility for FS with subsequent epilepsy maybe genetically distinct from susceptibility for afebrile seizures. A retrospective hospital-based study from Stockholm (Janszky et al, 2004) describes that MTLE has a tri-modal pattern of onset and also found that 35 % of MTLE patients had history of FS. Familial forms of MTLE have been described. A hospital-based retrospective study from Brazil (Kobayashi et al, 2001) found that 11 % of patients with familial MTLE had history of FS.

In a meta-analysis study done by Tonini C et al (2004) on 47 studies on the predictors of epilepsy surgery outcome, febrile seizures were strong predictors for a positive outcome. Abnormal MRI, concordance between neuroimaging and EEG, and extensive surgical resection were also positive indicators for seizure remission after surgery.

7.0 SUMMARY & CONCLUSION

In conclusion, a number of points can be summarised from this review of the literature in the past 15 years:

7.1 Mortality from FS:

- SFS do not carry a risk of death
- CFS carry a risk of death between 4-13% (from 5 studies), but it is often impossible in these studies to differentiate the contribution of the underlying cause from that of the FS.
- The overall mortality from FS (both SFS &CFS) when the literature is summated is very low (<1%) (summated mean risk from 29 studies)
- FSE in recent studies has been found to have a slightly higher mortality (1.6 %; summated mean risk from 3 studies) than in FS, and this has not apparently fallen over the past 3 decades (this is surprising and it is possible that is observation reflects and occult selection bias, with the current implementation of earlier treatment preventing milder cases evolving into FSE). Surprisingly too the risk of FSE reported in these studies is lower than the risk of death after CFS, but again this paradoxical result could reflect selection bias or the influence of the underlying condition.
- There is no suggestion in any of the literature that SUDEP occurs in association with FS, simple or complex.
- The longer the FSE duration, the worse the outcome.

7.2 Risk of later afebrile seizures and epilepsy:

- The summated mean risk (from 16 studies) of later afebrile seizures in FS patients is 5.3 % and 38% of the patients sustaining an afebrile seizure will later develop epilepsy.
- The risk of a later afebrile seizure in patients with CFS is higher – the risk from the two studies is 44 %.
- The risk of epilepsy after a FS increases with the duration of follow up, and has been found to lie between 2.5 % and 3.8 % (mean risks from 23 studies).
- The summated mean risk (from 5 studies) of epilepsy after a CFS is 17 %.
- In one very large prospective study with 23 years of follow-up, the cumulative risk of epilepsy after a FS was 6.9 % with 23 years of follow up compared to 1.8% in controls with no history of a FS. The rate of epilepsy is higher in those with FS in infancy or after the age of 3 years, then in those with FS onsets at age 1-3 years. In this study, the risk of subsequent epilepsy is also higher in those with a family history of epilepsy, cerebral palsy and low Apgar score at 5 minutes of birth. These risks do not seem to have fallen in the 3 decades since the NINDS study, and indeed may have slightly risen (although any rise may well be due to differences in methodology). It is also possible that the better early therapy of FS has reduced the number of seizures evolving into FSE and thus the cases of FSE now occurring are generally more severe than previously. Without knowing the proportion of cases of FS evolving to FSE, it is not possible to confirm this point.

7.3 Association of FS to HS/MTS:

- There is no evidence of any risk of HS/MTS in association with SFS.
- The summated risk of HS/MTS associated with CFS is 3 %. More than 83 % of CFS patients described in these studies had FSE. The range of risk is quite variable, and in part reflects variability in the duration of follow-up.
- There is a 39% risk (summated mean risk from 5 studies) of hippocampal or mesial temporal abnormalities on MRI immediately after a CFS. This high figure may be due largely to reversible, possibly oedematous, changes in the hippocampus during a PFS.
- In serial follow up MRI studies, the risk of significant hippocampal or mesial temporal abnormalities developing after longer follow up of CFS is 9 % (summated risk from 4 studies).
- The studies of medically refractory TLE patients show that 25 % (summated mean risk from 43 studies) have a history of febrile seizures.
- 44% of medically refractory TLE patients with HS/MTS have a history of febrile seizures (a summated mean risk from 35 studies).
- There are a number of associations reported with HS/MTS and with TLE following febrile seizures (in individual studies), including: medical intractability, good outcome following surgical therapy, post-ictal psychosis, severity and laterality of HS, and an association with the duration of the FS. Also, FS were found in several studies to more commonly result in epilepsy arising in the temporal lobe compared to other seizure locations.

8.0 FUTURE

There are 4 particular areas in the study of febrile seizures, which I consider are worth emphasis in the immediate future:

(i) Early AED Treatment: There is a suggestion that the definition of the 'duration' of SE should be shortened from the present cut-off of $\geq$30 minutes to $\geq$5 minutes, because any seizure lasting beyond 5 minutes is at 'high risk' to become refractory. This suggestion was made with the sole purpose of encouraging early treatment. This early treatment and the availability of a wider variety of AEDs are very likely to bring down the morbidity and mortality further in the new millennium.

(ii) Imaging studies: MRI imaging of the brain has markedly improved in the last decade. Prospective MRI studies of monozygotic twins and siblings of febrile seizure patients may give a clue to the link between FS and HS/MTS. Ethical and consent issues may make such a study difficult.

(iii) Genetic studies: Genes appear to be contributing to the risk of FS. For instance, studies have shown FS to be more common in relatives of individuals with past history of FS and in monozygotic twins compared with dizygotic twins. Mutations in the genes for subunits of the voltage-gated sodium channel and the γ2 subunit of the ligand-gated $GABA_A$ receptor were identified to patients suffering from generalised epilepsy with febrile seizure plus (GEFS+) (Baulac et al, 2004). Recent genetic linkage studies in large pedigrees and nuclear families with FS have identified five chromosomal regions (FEB1-FEB5) (Winawer and Hesdorrfer, 2004). Further studies are clearly required, particularly in large cohorts with appropriate controls, methodology and replication.

(iv) Novel approaches: Recent studies in young rat models of 8-11 days showed that hyperthermia leads to respiratory alkalosis which leads to epileptiform brain activity, but not

in the older rats of 22-23 days. This effect on epileptogenesis was blocked by increase in ambient carbon dioxide and also by intraperitoneal injection of bicarbonate (Schuchmann et al, 2006). This raises the question as to whether a strategy of increasing ambient carbon dioxide could help in preventing FS during the febrile episode. This would be worth studying in the clinical situation.

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APPENDIX A1

Table 1: Studies analysed for FS and mortality

Study	Author, Year, Journal,
Studies from database search: (n =14)	***Pubmed:*** Verity et al, 1993; British medical journal 307:225-8. Obi et al, 1994; Annals of Tropical Paediatrics 14:211-214. Lacroix et al, 1994; Critical care medicine 22(5):827-32. Cockerell et al, 1994; Lancet 344(8927): 918-21. Hauser et al, 1997; Epilepsia 38(12):1344-1349. Nadel et al, 1999; Journal of accident & emergency medicine 16(6):403-6. Maharshak and Somekh, 1999; Acta paediatrica 88:1279-83. Patja et al, 2000; The Pediatric Infectious Disease Journal 19(12):1127-34. Shinnar et al, 2001; Epilepsia 42(1):47-53. Kjaergaard et al, 2001; Archives of disease in childhood 85:236-239. Asadi-Pooya and Poordast, 2005; Epilepsy & Behavior 7(3):502-5. Chin et al, 2006; Lancet 368:222-9. Schanzer et al, 2006; The Pediatric Infectious Disease Journal 25(9):795-800. ***EmBase:*** Senanayake and Peiris, 1995; Seizure 4:273-277.
Studies from cross- references: (n =15)	Van Esch et al, 1996; Developmental medicine and child neurology 38:19-24. Scholtes et al, 1996; Seizure 5:177-184. Eriksson and Koivikko, 1997; Developmental medicine and child neurology 39:652-658. Mah and Mah, 1999; Pediatric neurology 20(5):364-69. Barnard and Wirrell, 1999; Journal of child neurology 14:787-794. MacDonald et al, 1999; European neurology 41:179-186. Lahat et al, 2000; British medical journal 321:83-6. Rainbow et al, 2002; Journal of paediatric child health 38:582-86.

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APPENDIX A2

Table 2: Studies analysed for FS and later risk of afebrile seizures/epilepsy

Study	Author, Year, Journal
Studies from Data base search (n = 32)	***Pubmed***: Verity et al, 1993; British medical journal 305: 225-8. Rosman et al, 1993; The New England journal of medicine 329:79-84. Pavone et al, 1993; Child's nervous system 9: 154-156. Laditan, 1994; Annals of Tropical Paediatrics 14: 303-308. Tsai and Hung, 1995; Journal of the Formosan Medical Association 94(6): 327-31. Nevo et al, 1995; Pediatric neurology 13(3): 235-241. Van Esch et al, 1996; Developmental medicine and child neurology 38(1): 19-24. Knudsen et al, 1996; Archives of disease in childhood 74: 13-18. Forsgren et al, 1997; Seizure 6: 21-26. Hackett et al, 1997; Developmental medicine and child neurology 39: 380-384. Tarkka et al, 1998; Neurology 18: 218-220. Berg et al, 1998; Epilepsia 39(1): 77-80. Pavlovic et al, 1998; European journal of neurology 6(1): 39-42. El-Radhi, 1998; European journal of paediatric neurology 2(2): 91-6. MacDonald et al, 1999; European neurology 41: 179-186. Webb et al, 1999; Pediatric neurology 20(4): 270-3. Sapir et al, 2000; Brain & Development 22: 484-486. Chang et al, 2000; Epilepsia 41(4): 412-420. Piperidou et al, 2002; The Journal of international medical research 30(6): 560-5. Kjeldsen et al, 2002; Epilepsy Research 51: 167-177. Tarkka et al, 2003; Neurology 60: 215-218. Borusiak and Herbold, 2003; Brain & Development 25: 272-274. Okumara et al, 2004; Brain & Development 26: 241-244.

	Yücel et al, 2004; Pediatrics International 46: 463-467. Vestergaard et al, 2004; The journal of American Medical Association 292: 351-357. Lee et al, 2004; Pediatric neurology 31: 157-164. Birca et al, 2005; European Journal of Paediatric Neurology 9: 339-45. Yu et al, 2007; Journal of Neuroscience Research 85: 166-172. Hussain et al, 2007; Seizure 16: 305-312. Vestergaard et al, 2007; American journal of epidemiology 165:911-918. ***Embase:*** Miyake et al, 1996; Epilepsia 37 (Suppl. 3): 72-73. Mauceri and Pavone, 2002; The Italian Journal of Pediatrics 28: 295-300.
Studies from cross-references: (n =1)	Metsäranta et al, 2004; Developmental medicine and child neurology 46: 4-8.

APPENDIX A3

Table 3: Studies analysed for association between FS and HS/MTS with MRI

Study	Author, Journal, Year
Studies from database search: (n = 70)	***Pubmed:*** Cendes et al, 1993; Neurology 43: 1083-1087. Kuks et al, 1993; Lancet 342: 1391-1394. Salanova et al, 1994; Neurology 51: 1008-1013. Hufnagel et al, 1994; Epilepsia 35(6): 1146-1153. Kodama et al, 1995; American journal of neuroradiology 16: 523-529. Harvey et al, 1995; Pediatric neurology 12: 201-206. Umbricht et al, 1995; The American journal of psychiatry 152: 224-231. Kuzniecky et al, 1996; Epilepsia 37(5): 433-439. Kanemoto et al, 1996; Neurology 47: 1199-1203. Davies et al, 1996; Epilepsy Research 24: 119-126. O'Brien et al, 1996; Brain 119:2133-2141. Harvey et al, 1997; Pediatric neurology 12: 201-206. Wang et al, 1997; Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 38(2):127-36. Breier et al, 1997; Neurology 48(4): 1047-1053. Barr et al, 1997; Journal of neurology, neurosurgery and psychiatry 63: 461-467. Van Paesschen et al, 1997a; Annals of neurology 43: 413-426. Bronen et al, 1997; American journal of roentgenology 169: 875-882. Van Paesschen et al, 1997b; Annals of neurology 42: 756-766. Kanemoto et al, 1998; Journal of neurology, neurosurgery and psychiatry 73:648-656. Schuh et al, 1998; Archives of neurology 55:1325-1328. VanLandingham et al, 1998; Annals of neurology 43: 413-426. Salanova et al, 1998; Acta neurologica scandinavica 98: 146-153. Kilpatrick et al, 1999; Epilepsia 40(7): 899-903.

	Choi et al, 1999; Epilepsia 40 (11):1634-1641. Davies et al, 1999; Neurology 52(8): 1717-1718. Kim Won-Joo et al, 1999; Epilepsia 40(3): 290-293. Szabó et al, 1999; Epilepsy Research 33: 1-9. Guerreiro et al, 1999; Epilepsia 40(4): 453-461. Lawson et al, 2000; Epilepsia 41(12):1540-1545. Bower et al, 2000; Journal of neurology, neurosurgery, and psychiatry 69:733-738. Kanemoto et al, 2000; Annals of neurology 47:571-574. Kobayashi et al, 2001; Neurology 56:166-172. Salmenperä et al, 2001; Epilepsy Research 46:69-82. Stephen et al, 2001; Epilepsia 42(3): 357-362. Briellmann et al, 2001; Neurology 57:1800-1804. Hennessy et al, 2001; Acta neurologica scandinavica 103: 344-350. Fuerst et al, 2001; Neurology 57:184-188. Moran et al, 2001; Brain 124:167-175. Grunewald et al, 2001; Journal of neurology, neurosurgery, and psychiatry 71:638-642. Scott et al, 2002; Brain 125:1951-1959. Thom et al, 2002; Journal of Neuropathology and Experimental Neurology 61(6): 510-519. Sztriha et al, 2002; Epilepsia 43(1):75-80. Pfänder et al, 2002; Epileptic disorders 4(3):185-195. Keller et al, 2002; Journal of neurology, neurosurgery, and psychiatry 73: 648-656. Janszky et al, 2003a; Seizure 12:550-554. Janszky et al, 2003b; Epilepsy Research 55:1-8. Janszky et al, 2003c; Neurology 60:1209-1210. Tarkka et al, 2003; Neurology 60:215-218. Kanemoto et al, 2003; Journal of neurology, neurosurgery, and psychiatry 64:245-248. Theodore et al, 2003; Archives of neurology 60:250-252. Hardy et al, 2003; Epilepsia 44(4):565-568. Scott et al, 2003; Brain 126:1-7. Janszky et al, 2004; Neurology 63: 1296-1298.

	Kalnins et al, 2004 ; Epilepsia 45(8):940-947. Carne et al, 2004 ; Brain 127:2276-2285. Xiao et al, 2004 ; Seizure 13:322-327. Theodore et al, 2004; Epilepsia 45(3): 276-279. Aaron et al, 2005; Journal of neurosurgery 102:902-909. Alessio et al, 2004; Epilepsy & Behavior 5:22-27. Thivard et al, 2005; NeuroImage 28:682-690. Wu Wen-Chau et al, 2005 ; American journal of neuroradiology 1270-1275. Chabardés et al, 2005 ; Brain 128:1818-1831. Yeni et al, 2005; European Journal of Neurology 12:103-107. Bernasconi et al, 2005; Neurology 65:223-228. Burneo et al, 2005; Epilepsy & behavior 7(3):486-90. Burneo et al, 2006; Archives of neurology 63:1106-1110. Labate et al, 2006; Neurology 66:562-565. Scott et al, 2006; Epilepsia 47(9):1493-1498. Farrow et al, 2006; Pediatric neurology 35:257-260. ***Embase :*** French et al, 1993 ; Annals of neurology 34:774-780.
Studies from cross-references (n=12)	Trenerry et al, 1993; Epilepsy Research 15:247-252. Abou-Khalil et al, 1993; Epilepsia; 34(5):878-883. Kuzniecky et al, 1993; Archives of neurology 50:65-9. Salanova et al, 1996; Brain 119: 989-996. Gil-Nagel and Risinger, 1997; Brain 120:183-192. Hamati-Haddad and Abou-Khalil, 1998; Neurology 50:917-922. Theodore et al, 1999; Neurology 52:132-136. Porter et al, 2003; Neurology 61: 365-368. Rosati et al, 2003; Neurology 60:1290-1295. Salanova et al, 2005; Acta neurologica scandinavica 111: 126-133. Natsume et al, 2007; Acta neurologica scandinavica 115 (Suppl. 186):25-28. Abou-Khalil et al, 2007; Epilepsy Research 73:104-110.

APPENDIX A4

Table 4: Mortality from FS [Raw Data]

Study: Number; Author, year; Population/ Hospital-based;	**Type of Febrile Seizure**	**Prospective or Retrospective study**	**Number of patients**	**Number of Deaths; (Mortality Rate)**
1.Verity,1993; (Population)	FSE	Prospective	19	0 %
2.Lacroix,1994; (Hospital)	FSE	Retrospective	21	0 %
3.Obi,1994; (Hospital)	FS	Prospective	202	7/202; (3.5 %)
4.Cockerell,1994; (Population)	FS	Prospective	220	0 %
5.Senanayake,1995; (Population) (1967-87)	FS	Retrospective	Not mentioned	396 deaths in a 20 Yr period.
6.Van Esch,1996; (Hospital)	FSE	Retrospective	57	0 %
7.Scholtes,1996; (Hospital)	FSE	Retrospective	5	0%
8.Eriksson,1997; (Hospital)	FSE	Retrospective	24	0 %
9.Hauser,1997; (Population)	FSE	Retrospective	17	0 %
10.Nadel,1999; (Hospital)	FSE	Retrospective	39	5 (MR12.8 %)

11.MacDonald,1999; (Population)	FS (Both SFS & CFS)	Prospective	207	0 %
12.Mah,1999; (Hospital)	FSE	Retrospective	18	0 %
13.Maharshak,1999; (Hospital)	FS	Retrospective	19	0 %
14.Barnard,1999; (Hospital)	FSE	Retrospective	13	0 %
15.Lahat,2000; (Hospital)	FSE	Prospective	47	0 %
16.Patja,2000; (Population)	FS	Prospective	52	0 %
17.Shinnar,2001; (Hospital)	FSE FS (Both SFS and CFS)	Prospective Prospective	180 244	0 % 0 %
18.Kjaergaard,2001; (Hospital)	FS	Retrospective	21	0 %
19.Rainbow,2002; (Hospital)	FS	Retrospective	46	0 %
20.Verroti,2004; (Hospital)	FS (Both SFS CFS)	Prospective	110	0 %
21.Metsäranta,2004;(Hospital)	FSE	Retrospective	116	0 %
22.Asadi-Pooya, 2005; (Hospital)	FSE	Retrospective	69	4 (MR 5.8%)

23.Maegaki,2005; (Hospital)	FSE	Retrospective	114	5 (MR 4.4%)
24.Chin,2006; (Population)	FSE	Prospective	56	0 %
25.Schanzer,2006; (Hospital)	FS	Retrospective	447	0 %
26.Takanashi,2006; (Hospital)	FSE	Retrospective	17	0 %
27.Hussain,2007; (Hospital)	FSE	Retrospective	47	0 %
28.Newland,2007; (Hospital)	FS	Retrospective	27	0 %
29.Nishiyama,2007; (Population)	FSE	Retrospective	17	0 %

Key:

FS Febrile Seizure
SFS Simple Febrile Seizure
CFS Complex Febrile Seizure
FSE Febrile Status Epilepticus

APPENDIX A5

Table 5: Risk of later afebrile seizures and epilepsy (recurrent afebrile seizure) in FS patients [Raw Data]

Study: Number; Author, year; Population/ Hospital-based;	**No. of patients**	**Follow-up period/ Study period**	**Prospective or Retrospective study**	**Afebrile seizure**	**Epilepsy (Recurrent afebrile seizures)**
1.Verity,1993; (Population)	FS 398	10 Yr	Prospective	4/398 ;(1 %)	
2.Rosman,1993; (Population)	FS 406	1.9 Yr	Prospective	21/406 ;(0.25 %)	
3.Pavone,1993; (Hospital)	FS 204 CFS 68	2 Yr 5 Yr	Retrospective	60/204 ;(33 %) 30/68 ;(57 %)	
4.Laditan,1994; (Hospital)	SFS 97 CFS 43	3 Yrs	Retrospective	17/97 ;(17.5 %) 19/43 ;(44.2%)	
5.Tsai,1995; (Hospital)	FS 154	7 Yr & 2 months	Prospective		19/154 ;(12.3 %)
6.Nevo,1995; (Hospital)	FS 84	1981-1990 (S.P)	Retrospective	15/84 ;(17.9 %)	
7.van Esch,1996; (Hospital)	FSE 57	2 Yr	Prospective		3/57 ;(5.3 %)
8.Miyake,1996; (Hospital)	FS 318	Not mentioned	Retrospective	38/318 ;(11.9 %)	
9.Knudsen,1996; (Hospital)	FS 272	12 Yr	Prospective		6/272 ;(2.2 %)
10.Forsgren,1997; (Population)	FS 92	6.7 Yrs	Prospective	4/92 ;(4.3 %)	3/92 ;(3.3 %)
11.Hackett,1997; (Home based survey)	FS 112	Not mentioned	Prospective		3/112 ;(2.7 %)

12.Tarkka,1998; (Hospital)	FS 156	2 Yr (S.P)	Prospective	2/156 ;(1.3 %)	
13.Berg,1998; (Hospital)	FS 428	29 months	Prospective	26/428 ;(6.1 %)	3/428 ;(0.7 %)
14.Pavlovic,1998; (Population)	FS 154	5 Yr	Retrospective	10/154 ;(6.5 %)	7/154 ;(4.5 %)
15.El-Radhi, 1998; (Hospital)	FS 132	2 Yr	Retrospective	5/132 ;(3.8 %)	3/132 ;(2.3 %)
16.MacDonald,1999; (Population)	FS 207	11.2 Yr	Prospective		12/207 ;(6 %)
17.Webb,1999; (Hospital)	FS 50	5 Yr and 6 months	Retrospective	5/50 ;(10 %)	
18.Sapir,2000; (Hospital)	CFS 48	43 months (mean)/ 1991-1998 (S.P)	Retrospective		13/48 ;(27.1 %)
19.Chang,2000; (Population)	FS 87	6 Yr	Prospective		4/87 ;(4.6 %)
20.Piperidou,2002; (Population)	FS 56	Not mentioned	Retrospective	2/56; (3.6 %)	2/56 ;(3.6 %)
21.Kjeldsen,2002; (Population)	FS 678	12-40 Yr	Retrospective		51/678; (7.5 %)
22.Mauceri,2002 (Population)	FS 180	25-30 Yr	Retrospective		10/180; (5.5 %)
23.Borusiak, 2003; (Hospital)	FS 82	14-28 months	Prospective		5/82; (6.1 %)
24.Tarkka, 2003; (Hospital)	FS 329	8-15 Yr	Prospective	8/329 ;(2.4 %)	
25.Okumara, 2004; (Hospital)	FS 43	>3Yr / 1995-1997 (S.P)	Retrospective	2/43 ;(4.7 %)	

26.Metsäranta, 2004; (Hospital)	FSE 116	25 months(mean)	Retrospective		5/116 ;(4.3 %)
27. Yucel, 2004 ; (Hospital)	CFS 159	6 months-7 Yr	Retrospective		51/159 ;(32.1 %)
28. Vestergaard, 2004; (Population)	FS 17986	1991-99/ 105 months (S.P)	Prospective		355/17,986 ;(2%)
29. Lee, 2004 ; (Hospital)	FS 1170	1980-93	Retrospective	3/1170 ;(0.3 %)	1/1170 ;(0.1 %)
30.Birca, 2005; (Hospital)	FS 482	5 Yr/ 1977-1987	Retrospective		37/482 ;(7.7 %)
31. Yu, 2007; (Hospital)	FS 60	1-5 Yr	Prospective		11/60; (18.3 %)
32.Hussain, 2007; (Hospital)	CFS 47	1999-2004	Retrospective		1/47 ;(2.1 %)
33.Vestergaard, 2007; (Population)	FS 49857	23 Yr/1978-2005	Prospective		2149/49857; (4.3 %) CI- 6.9 % (23 Yrs after the first FS)

Key:

FS	Febrile Seizure
SFS	Simple Febrile Seizure
CFS	Complex Febrile Seizure
FSE	Febrile Status Epilepticus
CI	Cumulative Incidence
S.P	Study Period
AED	Anti Epileptic Drug

APPENDIX A6

Table 6.11: Hippocampal / Mesial temporal abnormality developing immediately after CFS [Raw Data]

Study: Number; Author, year; **Population/ Hospital-based;** **Follow-up;**	**Number of FS patients**	**Type of study**	**Hippocampal or Mesial temporal Abnormalities developing in FS patients**	**Conclusion of the study**
1.VanLandingham,1998; Hospital; Prospective; 1994- 1997	CFS 27	MRI was done soon after CFS	6/27 (22.2 %) had increased hippocampal T2 intensity and volume suggestive of oedema; 2 of them had HA and both had Perinatal insults. All 6 had FSE.	(a)CFS may produce acute insult to the hippocampus which may later evolve into hippocampal atrophy in a few patients. (b)Few of the CFS maybe related to pre-existing brain dysfunction.
2.Szabó,1999; Hospital; Prospective;	CFS 5	MRI done between 2days and 46 months after CFS	All (100 %) had smaller total hippocampal volumes and larger right to left HV ratios and one of them had significant hippocampal asymmetry. One had FSE.	Three possibilities- (a)developmental abnormality, (b)Injury during CFS & (c) Age related change.
3.Grunewald, 2001; Hospital; Prospective; 1995-1999	CFS 13	MRI was done within 14 days of the convulsion.	10 of the 13 CFS patients (76.9 %) had hippocampal asymmetry. HVR (larger/smaller hippocampus) was greater in the FS group with respect to controls and afebrile seizures. 9 of the patients who developed abnormality had FSE.	There is high prevalence of structural brain abnormalities within 2 weeks of FS especially hippocampal asymmetry.

4.Scott, 2002; Hospital; Prospective;	CFS 21 (PFS)	MRI was done within 5 days of the event.	2 of the 21 CFS patients (9.5 %) had hippocampal asymmetry quantitatively but none had MTS. All patients had FSE.	PFS is associated with hippocampal oedema in the acute phase which resolves in 5 days.
5.Natsume, 2007; Hospital Prospective; 2004-2005	CFS 12 (PFS)	Initial MRI done within 5 days of PFS	7/12 (58.3 %) with PFS of more than 60 minutes had larger HV than controls. 3 of them also had transient DWI hyperintensity. All patients had FSE.	PFS of more than 60 minutes was associated with larger HV and transient DWI hyper intensity.

KEY

FS	Febrile Seizure
SFS	Simple Febrile Seizure
CFS	Complex Febrile Seizure
DWI	Diffusion Weighted Imaging
FSE	Febrile Status Epilepticus
HA	Hippocampal Atrophy
HV	Hippocampal Volume
HVR	Hippocampal Volume Ratio
MRI	Magnetic Resonance Imaging
MTS	Mesial Temporal Sclerosis
PFS	Prolonged Febrile Seizure

APPENDIX A7

Table 6.12: Hippocampal / mesial temporal lobe abnormality followed up with serial MRI scans [Raw Data]

Study: Number; **Author, year;** **Population/ Hospital-based;**	**Number of patients with CFS/ hippocampal / and or mesial temporal lobe abnormality**	**Follow-up Period**	**HS/MTS**	**Conclusion of the study**
1.Tarkka,2003; Hospital; Prospective;	CFS (PFS) 32	12.3 Yrs follow-up	None of them Developed MTS	The chance of developing MTS is low even after PFS.
2.Scott,2003; Hospital; Prospective;	CFS 14 (PFS)	MRI was done within 5 days of PFS and was repeated after 4-8 months follow-up	5 of them developed hippocampal asymmetry outside the 95th percentile but there was no T2 relaxation abnormality.	This could be due to- (a)These patients maybe in lag period for the development of MTS. (OR) (b)The asymmetry could be due to return to the original hippocampal abnormality that existed before the post-acute oedema.
3.Scott,2006; Hospital; Prospective;	CFS 23 (PFS)	MRI was done within 5 days of PFS and repeated after 5.5 months.	(a)Apparent Diffusion Coefficient (ADC) declined in patients between the acute and follow-up MRI in only patients who were investigated within 2	(a)PFS is associated with hippocampal oedema in the acute phase which is vasogenic in nature. (b) A pre-existing hippocampal abnormality may predispose individuals to have a PFS.

			days of PFS. (b)Age dependent decline in ADC was not noticed in PFS patients.	
4.Farrow,2006; Hospital; Prospective;	CFS 8 (PFS)	6.5 Yrs (mean) between MRI scans	2/8 (25 %) developed HS.	Complicated FS may lead to HS, if initial imaging was associated with hippocampal asymmetry.

KEY

ADC	Apparent Diffusion Coefficient
CFS	Complex Febrile Seizure
FS	Febrile Seizure
HS	Hippocampal Sclerosis
MRI	Magnetic Resonance Imaging
MTS	Mesial Temporal Sclerosis
PFS	Prolonged Febrile Seizure

APPENDIX A8

Table 6.21: History of FS in TLE patients with HS/MTS [Raw Data]

Study: Number; Author, year; Population/ Hospital-based; Type of Study	**Number of TLE patients studied with HS / MTS**	**Aim of the study**	**Number of TLE patients with history of FS**	**Conclusion of the study**
1.Kuks,1993; Hospital;	Refractory epilepsy + HVL 45	Volumetric MRI of refractory epilepsy	16/45; (35.6 %)	Significant association between FS and diffuse HVL
2.Harvey,1995; Hospital;	TLE + HS 30	Pre-surgical evaluation for Anterior temporal lobectomy	17/30; (56.7 %)	HS may cause TLE
3.Davies,1996; Hospital;	TLE + HS 122	Pre-surgical evaluation for Anterior temporal lobectomy	39/122; (32 %)	(a) Positive correlation between severe HS and a history of FS. (b) Inverse correlation between age of seizure onset and severity of HS. (c)Positive correlation between duration of epilepsy and severity of HS.
4.O'Brien,1996; Hospital;	TLE + MTS 31	Pre-surgical evaluation for temporal lobectomy	18/31; (58.1 %)	MTS patients had a better seizure-free post-surgical outcome.
5.Kuzniecky,1996; Hospital;	TLE + MTS 47	Pre-surgical evaluation for temporal lobectomy	26/47; (55.3 %)	Focal HA was more common in those with a history of CFS.
6.Kanemoto,1996; Hospital;	TLE + HS 61	Study the history and clinical course of non-lesional TLE	31/61; (50.8 %)	HS was associated with psychosis and history of CFS

7.Bronen,1997; Hospital; Retrospective;	TLE + HS 55	Pre-operative MRI evaluation of TLE	28/55; (50.9 %)	History of FS was significantly associated with HS.
8.Van Paesschen, 1997a; Hospital;	TLE + HS 48	To study the spectrum of HS in TLE patients.	21/48; (43.8%)	FS was associated with unilateral HS but not bilateral HS.
9.Van Paesschen, 1997b; Hospital;	TLE + HS 52	To study the relationship between T2 relaxation time and hippocampal volume to neuronal and glial cell layers of hippocampus	32/52; (61.5 %)	Hippocampal atrophy in HS was associated with neuronal cell depletion and concomitant gliosis.
10.Kilpatrick,1999; Hospital; Prospective; 38 months	TLE + HS 56	Pre-operative MRI evaluation of TLE	34/56; (60.7 %)	Seizure frequency and duration of epilepsy are not risk factors for postoperative seizure recurrence.
11.Davies,1999; Hospital;	TLE + HS 105	To find the association between FS and HS in patients who underwent temporal lobectomy.	46/105; (43.8 %)	Left HS is more common with history of FS. There maybe other mechanisms also which leads to HS.
12.Choi,1999; Hospital; Prospective; 1995-1997	TLE + HS 56	Pre-operative MRI evaluation of TLE. To study the white matter changes in the anterior temporal lobe and its clinico-pathological correlations.	20/56; (35.7 %)	WMC was associated with hypometabolism of temporal lobe on PET and larger number of heterotopic neurons in histopathology. They also had earlier seizure onset and past history of FS.
13.Kim,1999; Hospital; Prospective; 1996-1998	TLE + MTS 104	To study the long term prognosis of MTS patients	37/104; (35.6 %)	MTS associated with FS and EEG changes responded poorly to AEDs.
14.Bower,2000; Hospital;	TLE + HS 77	Pre-surgical evaluation for Anterior temporal lobectomy	37/77; (48 %)	Febrile seizures do not cause more severe HS. So HS maybe a pre-existing abnormality.

15.Kanemoto,2000; Hospital;	TLE + HS 50	To study the Interleukin-1 (IL-1) gene polymorphisms was responsible for TLE with HS.	37/50; (74 %)	In homozygotes for IL-1β-511*2, minor antecedents like FS could set up a stream of events that can lead to HS.
16.Stephen,2001; Hospital;	TLE + MTS 73	To study the effectiveness of AED in localisation related epilepsy	27/73; (37 %)	MTS related seizures responded poorly to AED when compared with other pathologies.
17.Briellmann,2001; Hospital;	TLE + HS 66	Pre-surgical evaluation for anterior temporal lobectomy.	43/66; (65 %)	Family history of FS is a risk factor for TLE with HS.
18.Hennessy,2001; Hospital; Retrospective;	TLE + MTS 116	To assess the risk factors that determines the seizure remission following epilepsy surgery. Pre-surgical evaluation for anterior temporal lobectomy.	56/116; (48.3 %)	Favourable outcome was seen if the interictal EEG localized to the operated lobe and if secondary generalisation of the partial seizure was not present. Poor outcome was seen in those with perinatal insults to the brain.
19.Fuerst,2001; Hospital; Retrospective;	TLE + HS 46	To study the association between the age of onset and duration of seizure disorder with severity of HS and TLE.	17/46; (37 %)	Earlier onset and hence the duration of the seizure disorder was associated with severe HS.
20.Moran, 2001; Hospital; Retrospective;	TLE + MTS 62	To study abnormalities in the temporal lobe in TLE patients with MTS.	37/62; (59.7 %)	Degree of atrophy outside the hippocampus is related to the degree of hippocampal atrophy and was not associated with an antecedent history of FS.
21.Thom, 2002; Hospital; Retrospective; 1993-2000	TLE + HS 183	To study the correlates of the cytoarchitectural abnormalities noted in HS.	30/183; (16.4 %)	Severity of granule cell disorganization correlated with severity of hippocampal neuronal loss but not with antecedents like FS.
22.Janszky, 2003a; Hospital; Retrospective; 1994-2002	TLE + HS 243	Pre-surgical evaluation for TLE	115/243; (47.3 %)	Presence of bilateral interictal discharges was associated with earlier onset of TLE.

23.Janszky,2003b; Hospital; Retrospective; 1994-2002	TLE + HS 133	Pre-surgical evaluation for anterior temporal lobectomy.	36/133; (27.1 %)	Patients with FS history has better surgical outcome in a 2 yr follow-up of 84 patients.
24.Janszky,2003c; Hospital; Retrospective; 1995-2002	TLE + HS 292	Pre-surgical evaluation for anterior temporal lobectomy.	137/292; (47 %)	Right HS was more common with history of FS.
25.Hardy, 2003; Hospital; Prospective; 1998-1999	TLE + MTS 118	To study the factors which affect the outcome of surgery for MTS.	30/118; (25.4 %)	History of status epilepticus determined a poorer outcome after surgery.
26.Kanemoto, 2003; Hospital; Retrospective; 1999-2001	TLE + HS 66	To study the high frequency of Interleukin (IL)-1β-511 T allele in TLE patients with HS.	35/66; (53 %)	Patients with HS had significantly higher frequency of antecedent of PFS than TLE without HS. There was a higher chance of the IL-1β-511 T allele in PFS when compared to SFS.
27.Xiao,2004; Hospital; Retrospective; 1991-2000	TLE + HS 268	Pre-surgical evaluation of epilepsy patients.	76/268; (28.4 %)	FS was the second most common antecedent in HS patients after trauma.
28.Kalnins,2004; Hospital;	TLE + HS 140	To study the significance of the subtle abnormalities found in some patients with HS. Pre-surgical evaluation for anterior temporal lobectomy.	52/140; (37.1 %)	Around 40 % had subtle abnormalities but were not associated with antecedents like FS or the histological pattern of HS.
29.Carne,2004; Hospital; Retrospective;	TLE + HS 30	To study the characteristics of nonlesional TLE with respect to TLE with HS.	13/30; (43.3 %)	The nonlesional TLE may involve abnormalities in the lateral temporal pole rather than mesial structures.
30.Thivard,2005; Hospital;	MTLE + HS 35	Pre-surgical evaluation for anterior temporal lobectomy.	22/35; (62.9 %)	Diffusion abnormalities not restricted to the pathologic hippocampus.

31.Aaron,2005; Hospital;	TLE + MTS 50	To study the characteristics of MTLE with normal MRI and Histopathology.	17/50; (34 %)	MTLE without FS (Paradoxical TLE) have less chance of antecedent FS than the classical MTLE with MTS.PTLE patients tended to have later onset of epilepsy, have less neuronal loss but poorer prognosis after surgery.
32.Burneo,2005; Hospital; Retrospective; 1998-2003	TLE + MTS 70	Pre-surgical evaluation for Anterior temporal lobectomy.	26/70; (38 %)	African-Americans had a poorer seizure free outcome after surgery
33.Yeni,2005; Hospital; Retrospective	TLE + HS 47	To study the relationship between apolipoprotein E (APOE) polymorphisms and MTLE with HS and the latency for epilepsy to develop.	32/47; (68 %)	No association was found between APOE and MTLE with HS.
34.Burneo,2006; Hospital; Prospective;	TLE + MTS 252	Pre-surgical evaluation for Anterior temporal lobectomy.	176/252; (69.8 %)	The sex of the patient may play a role in the outcome of surgery.
35.Labate,2006; Hospital;	TLE + MTS 39	MRI study of sporadic benign temporal lobe epilepsy.	9/39; (23.1 %)	History of FS was more frequent in patients with MRI-detectable MTS than those with normal.

Key:

FS Febrile Seizure
CFS Complex Febrile Seizure
AED Anti Epileptic Drug
HVL Hippocampal Volume Loss
MTS Mesial Temporal Sclerosis
TLE Temporal Lobe Epilepsy
HS Hippocampal Sclerosis
MRI Magnetic Resonance Imaging
PTLE Paradoxical Temporal Lobe Epilepsy

APPENDIX A9

Table 6.22: History of FS in TLE patients [Raw Data]

Study: Number; Author, year; Population/ Hospital-based; Type of Study	**Number of TLE Patients**	**Aims of the study**	**Number of TLE patients with history of FS**	**Conclusion of the study**
1.Cendes,1993; Hospital; Retrospective; 1991-1992.	TLE 43	Pre-surgical evaluation for anterior temporal lobectomy.	15/43; (34.9 %)	PFS was associated with more severe MTS w.r.t those without a history of FS.
2.Trenerry,1993; Hospital; Retrospective;	TLE 128	Pre-surgical evaluation for anterior temporal lobectomy.	53/128; (41.4 %)	Hippocampal atrophy is associated with earlier onset of recurrent seizures in left temporal patients.
3.Abou-Khalil,1993; Hospital; Retrospective; 1983-1985	TLE 47	Pre-surgical evaluation for temporal lobectomy.	19/47; (40.4 %)	Outcome of patients with past history of FS was better after temporal lobectomy than those without such a history.
4.Kuzniecky,1993; Hospital; Prospective; 22 months	TLE 34	To study the value of MRI in predicting the prognosis of epilepsy surgery outcome.	13/34; (38.2 %)	Abnormal MRI especially hippocampal atrophy and antecedent FS had a better surgical outcome.

5.French,1993; Hospital; Retrospective;	MTLE 67	To define the MTLE syndrome in patients who were evaluated for pre-surgically for epilepsy surgery.	45/67; (67.2 %)	Strong association between CFS and later MTLE.
6.Salanova,1994; Hospital; Retrospective; 1984-1992	TLE 98	Pre-surgical evaluation for temporal lobectomy.	29/98; (29.6 %)	Better surgical outcome in those patients with history of FS and MTS.
7.Hufnagel,1994; Hospital; Retrospective;	TLE 59	The study aimed to see the significance of epileptiform activity in TLE as part of pre-surgical evaluation.	12/59; (20.4 %)	Patients with lateralization of seizure origin and inter-ictal epileptiform potentials had excellent seizure outcome after surgery.
8.Kodama,1995; Hospital;	TLE 38	MRI study with TLE in a psychiatry department.	9/38; (23.7 %)	CFS can be associated with MTS.
9.Harvey,1995; Hospital;	TLE 56	Pre-surgical evaluation for anterior temporal lobectomy.	22/56; (39.3 %)	HS may cause TLE
10.Umbricht,1995; Hospital;	TLE 44	To study the clinical, neuropsychological, and seizure types to psychoses in TLE patients. Pre-surgical evaluation for epilepsy surgery.	15/44; (34.1 %)	TLE patients with bitemporal seizure foci, absence of FC and a history of clustering of seizures are prone to develop psychosis.
11.Salanova,1996; Hospital; Retrospective;	TLE 300	To study the characteristics of 'running down' phenomenon in TLE after surgery.	70/300; (23.3 %)	Patients with running down phenomenon will have intermediate size epileptogenic areas.
12.Kanemoto,1996; Hospital; 1991-1994	TLE 50	Study the history and clinical course of non-lesional TLE.	16/50; (32 %)	HS was associated with psychosis and history of CFS.
13.Barr,1997; Hospital;	TLE 44	Evaluation of hippocampal volume reduction in TLE with and without history of FS.	21/44; (47.7 %)	History of FS is associated with smaller hippocampus on the side of seizure focus in TLE.

14.Harvey,1997; Population; Prospective; 1991-1993	TLE 63	To study the natural evaluation of TLE.	13/63; (21 %)	Association is there between HS and significant antecedents.
15.Wang,1997; Hospital;	TLE 31	To study the brain lesions in symptomatic and cryptogenic partial epilepsies in children.	9/31; (29 %)	MTS associated with past history of FS and TLE.
16.Breier,1997 Hospital;	TLE 34	The study tried to look at the effects of duration of epilepsy on cerebral perfusion and metabolism using PET in patients as part of pre-surgical evaluation.	5/34; (14.7 %)	The study suggested that inter-hemispheric asymmetries in blood flow and glucose metabolism are related to the duration of seizure.
17.Gil-Nagel, 1997; Hospital; Retrospective;	TLE 35	To study the ictal semiology in hippocampal versus extra hippocampal TLE.	13/35; (37.1 %)	Antecedent FS was present only in the hippocampal TLE.
18.Hamati-Haddad,1998; Hospital;	TLE 310	To study if there is any preferential involvement of temporal localization with antecedent FS.	78/310; (25.2 %)	There is a preferential involvement of temporal lobe after FS.
19.Kanemoto,1998; Hospital; Retrospective; 1987-1993	TLE 449	To study the correlation between CFS and MTLE and find the characteristics of TLE with CFS.	104/449; (23.2 %)	TLE with history of CFS are associated with early onset of seizures, autonomic auras and MTS on MRI.They also had better post surgical results.
20. Schuh,1998; Hospital; Retrospective;	TLE 102	To study the risk factors for epilepsy in prognosing the outcome of epilepsy surgery.	39/102; (38.2 %)	Head trauma was associated with bad prognosis with surgical outcome in terms of seizures. Antecedent FS did not affect the prognosis.
21.Salanova,1998; Hospital; Retrospective; 1994-1996	TLE 38	Pre-surgical evaluation for temporal lobectomy.	17/38; (44.7 %)	MRI-HS correlated with history of febrile seizures and pathologically demonstrated HS.FDG-PET is also useful like MRI.

22.Guerreiro,1999 ; Hospital; Retrospective;	TLE 65	To correlate clinical features to different patterns of hippocampal and amygdalar abnormalities.	19/65; (29.2%)	HA was associated with earlier seizures. It was also associated with history of FS and memory deficits.
23.Davies,1999; Hospital; Retrospective;	TLE 168	To find the association between FS and HS in patients who underwent temporal lobectomy.	52/168; (40 %)	Left HS is more common with history of FS. There maybe other mechanisms also which leads to HS.
24.Theodore,1999; Hospital;	TLE 35	To study whether epilepsy duration is related to HA.	9/35; (25.7%)	CFS especially PFS was associated with smaller hippocampal volume.
25.Lawson,2000; Hospital; Retrospective, 1995-1999.	Paediatric epilepsy 231	Pre-surgical evaluation for temporal lobectomy.	44/231; 19 %	Hippocampal volume ratio (HVR) was associated with complex FS but not simple FS.
26.Kobayashi,2001; Hospital; Retrospective, 1997- 1999.	MTLE 98	Pre-surgical evaluation for temporal lobectomy.	11/98; (11 %)	No relationship between HA and severity of epilepsy in familial MTLE
27.Salmenperä,2001; Hospital; 1993-1996	TLE 153	MRI study of hippocampal and amygdalar volumes in partial epilepsy.	9/153; (5.9 %)	CFS, frequent seizures and early onset of seizures are associated with HVL in TLE patients.
28.Sztriha,2002; Population; Prospective; 1995-1999.	TLE 30	Community based cohort.	5/30; (16.7 %)	TLE with HS has greater risk of continued seizures and psychological problems.

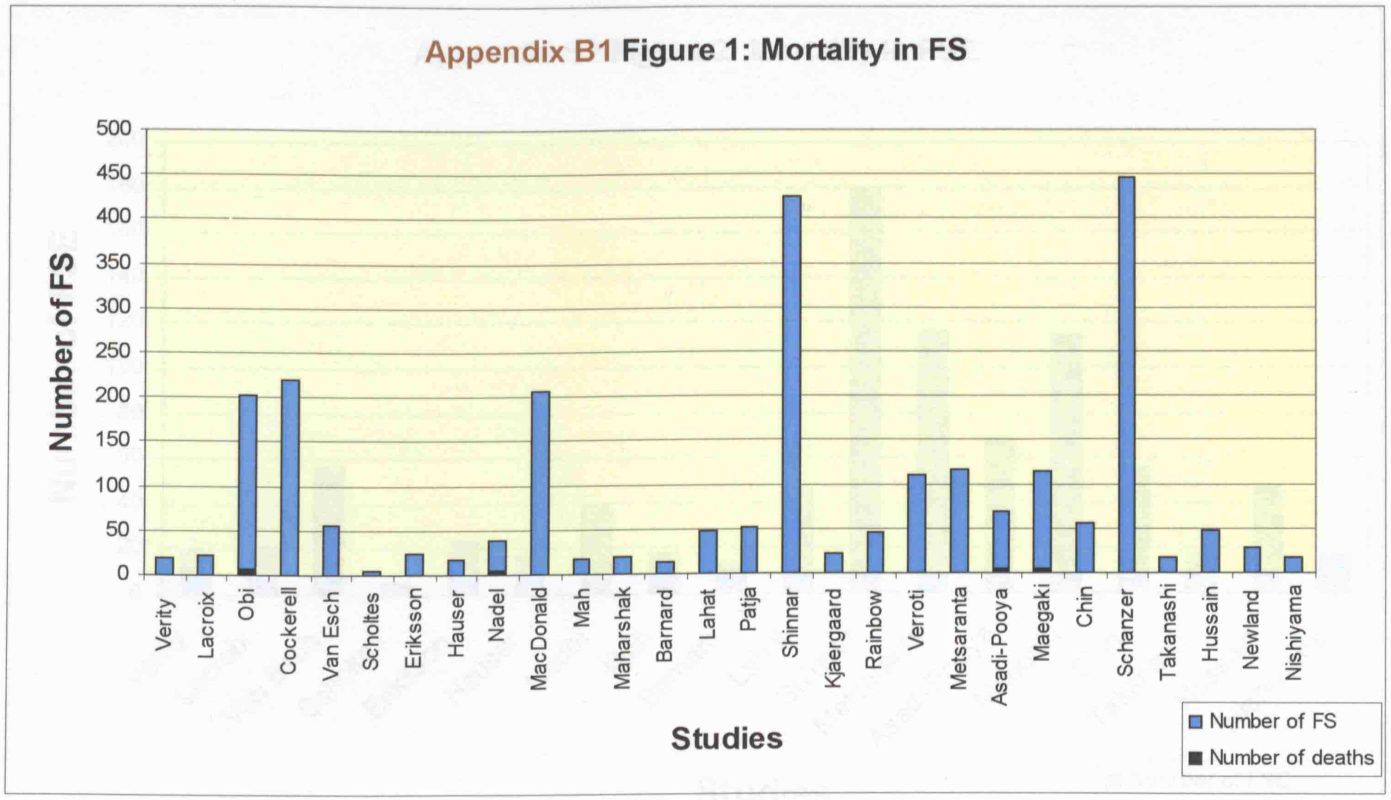
29.Pfänder,2002; Hospital; Prospective; 1991-1998	MTLE 86	To evaluate whether MTLE and Neo-cortical TLE (NTE) can be distinguished on electro-clinically in pre-surgically evaluated patients.	25/86; (29.1 %)	History of FS, abdominal auras and contralateral hand dystonia are more common in MTLE than NTE.
30.Keller,2002; Hospital;	TLE 116	The study was aimed at using voxel based morphometric and stereological analysis for studying brain morphology in medically refractory TLE. Pre-surgical evaluation for temporal lobectomy.	40/116; (34.5 %)	Patients who had history of FS had smaller hippocampal volumes than those without such a history.
31. Theodore et al,2003; Hospital; Retrospective;	MTLE 40	To study the total cerebral volumes in MTLE with and without antecedent FS.	9/40; (22.5 %)	CFS was associated with reduced total cerebral volume especially males.
32. Porter,2003; Hospital; Retrospective; 1992-2000	TLE 33	To study the risk factors for TLE. Pre-surgical evaluation for temporal lobectomy.	15/33; (45.5 %)	Cortical dysplasia was seen in 2/3rd of the TLE patients who under went epilepsy surgery.
33. Rosati,2003; Hospital; Retrospective;	TLE 31	To study the characteristics of nonlesional TLE with rare interictal abnormalities and which is refractory to medical treatment.	10/31; (32.3 %)	The group of patients with TLE but rare spikes on EEG and who are refractory to AED may represent a less severe form than with frequent spikes.
34.Theodore,2004; Hospital; Retrospective;	Partial Epilepsy 91	To study the influence of antecedent risk factors on the functional changes in the hippocampus.	26/91; (28.6 %)	Longer duration of epilepsy was associated with greater hypometabolism ipsilateral to the seizure foci in the brain.
35.Alessio,2004; Hospital;	MTLE 35	Neuropsychological evaluation of MTLE patients.	4/35; (11.4 %)	Hippocampal atrophy (HA) was associated with memory deficits. Deficits in verbal memory maybe associated with left HA.

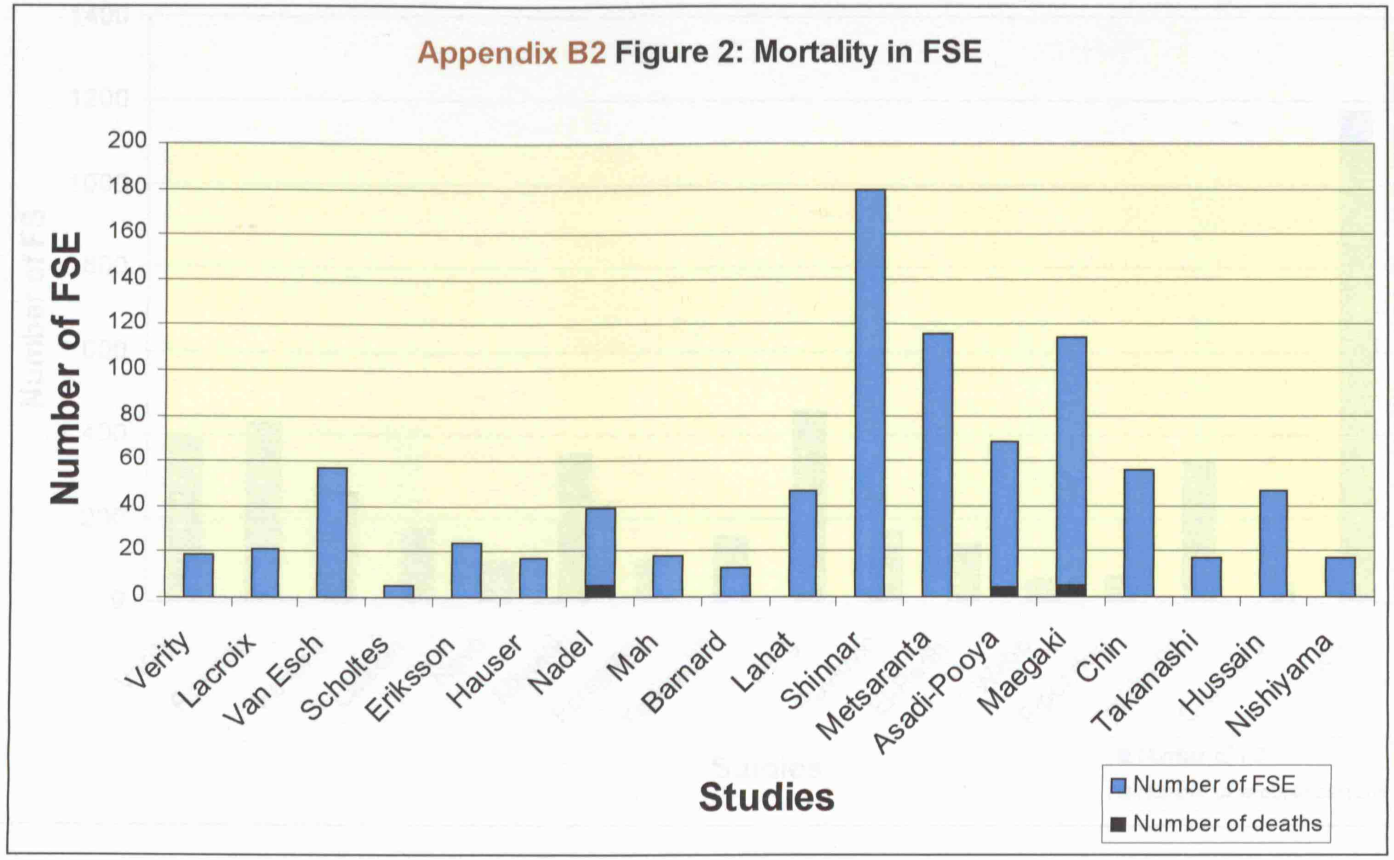
36.Janszky;2004; Hospital; Retrospective; 1993-2003	MTLE 118	Pre-surgical evaluation for temporal lobectomy.	41/118; (34.7 %)	Age at onset of epilepsy with HS preceded by past history of febrile seizures.
37.Carne,2004; Hospital; Retrospective;	TLE 30	To study the characteristics of nonlesional TLE with respect to TLE with HS.	1/30; (3 %)	The nonlesional TLE may involve abnormalities in the lateral temporal pole rather than mesial structures.
38.Xiao,2004; Hospital; Retrospective, 1991-2000	TLE 904	Pre-surgical evaluation of epilepsy patients.	103/904; (11.4 %)	FS was the second most common aetiology after trauma in TLE patients.
39.Wu,2005; Hospital;	TLE 39	Pre-surgical evaluation for anterior temporal lobectomy.	22/39; (56.4 %)	Children with TLE and FS had lower hippocampal volumes than those without FS history.
40.Chabardés,2005; Hospital;	TLE 48	Study the role of temporal pole in the drug refractory TLE. Pre-surgical evaluation for temporal lobectomy.	22/48; (45.8 %)	Frequent temporal pole involvement is seen at the onset of TLE seizures.
41.Salanova,2005; Hospital;	TLE 262	Pre-surgical evaluation for temporal lobectomy.	82/262; (31.3 %)	TLE patients with history of FS and abnormal imaging are more likely to be seizure free after lesional surgery.
42.Bernasconi,2005; Hospital;	TLE 86	To study the relationship between atrophy of mesial temporal structures and duration of epilepsy, presence of secondary generalised seizures and prolonged febrile seizures. Pre-surgical evaluation for temporal lobectomy.	30/86; (34.9 %)	Patients with history of FS had smaller hippocampal volumes.

43.Abou-Khalil,2007; Hospital; Prospective;	TLE 773	Evaluation of established epilepsy patients in an epilepsy clinic.	188/773; (24.3 %)	Susceptibility for FS with subsequent epilepsy maybe genetically distinct from susceptibility for afebrile seizures.

KEY:

CFS	Complex Febrile Seizure
FS	Febrile Seizure
HA	Hippocampal Atrophy
HS	Hippocampal Sclerosis
HVL	Hippocampal Volume Loss
HVR	Hippocampal Volume Ratio
MRI	Magnetic Resonance Imaging
MTLE	Mesial Temporal Lobe Epilepsy
MTS	Mesial Temporal Sclerosis
NTLE	Neo-cortical Temporal Lobe Epilepsy
PET	Positron Emission Tomography
PFS	Prolonged Febrile Seizure
TLE	Temporal Lobe Epilepsy


Appendix B1 Figure 1: Mortality in FS
Number of FS
500
450
400
350
300
250
200
150
100
50
0
Verity
Lacroix
Obi
Cockerell
Van Esch
Scholtes
Eriksson
Hauser
Nadel
MacDonald
Mah
Maharshak
Barnard
Lahat
Patja
Shinnar
Kjaergaard
Rainbow
Verroti
Metsaranta
Asadi-Pooya
Maegaki
Chin
Schanzer
Takanashi
Hussain
Newland
Nishiyama
Studies
Number of FS
Number of deaths


Appendix B2 Figure 2: Mortality in FSE
Number of FSE
200
180
160
140
120
100
80
60
40
20
0
Verity
Lacroix
Van Esch
Scholtes
Eriksson
Hauser
Nadel
Mah
Barnard
Lahat
Shinnar
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Asadi-Pooya
Maegaki
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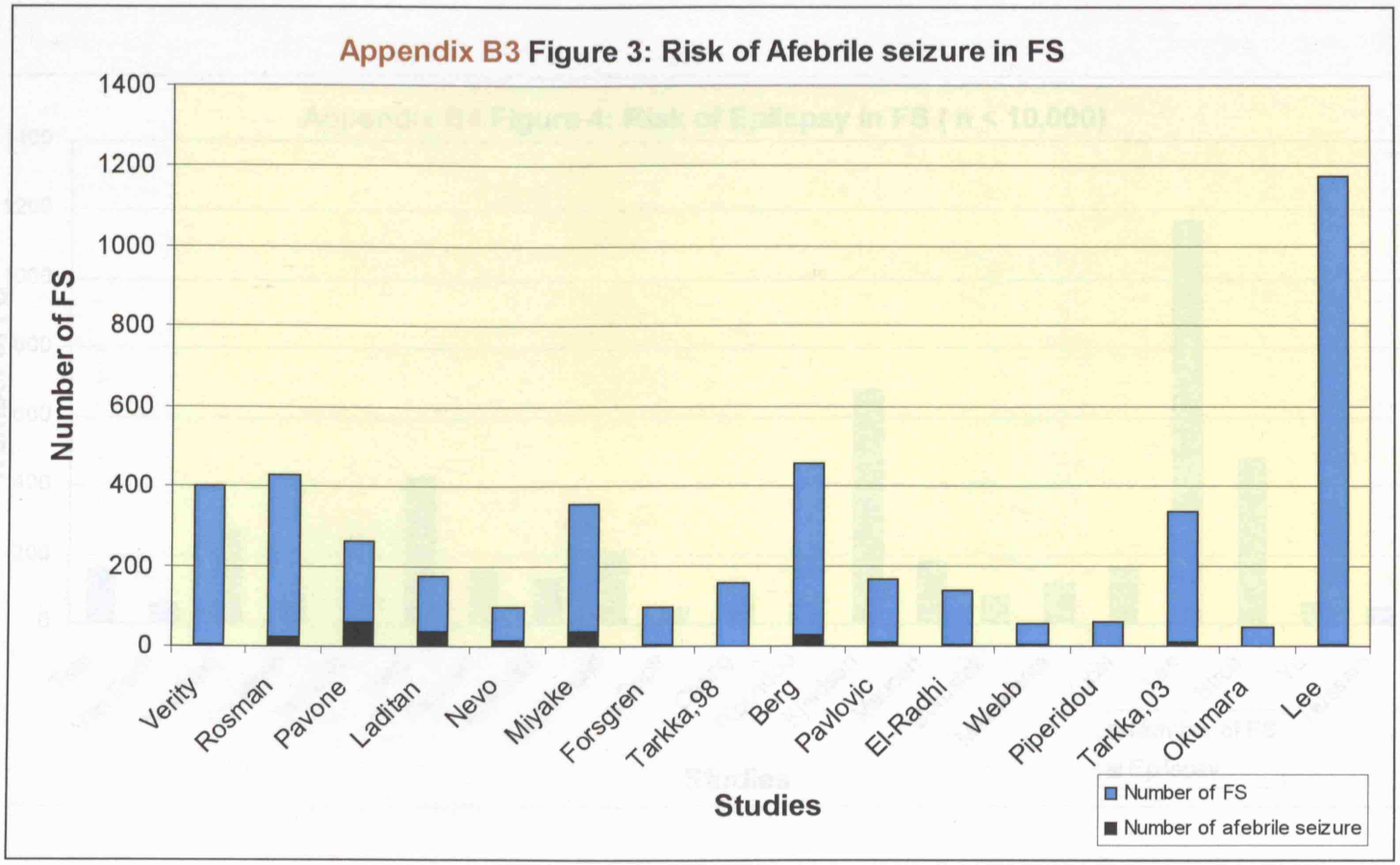
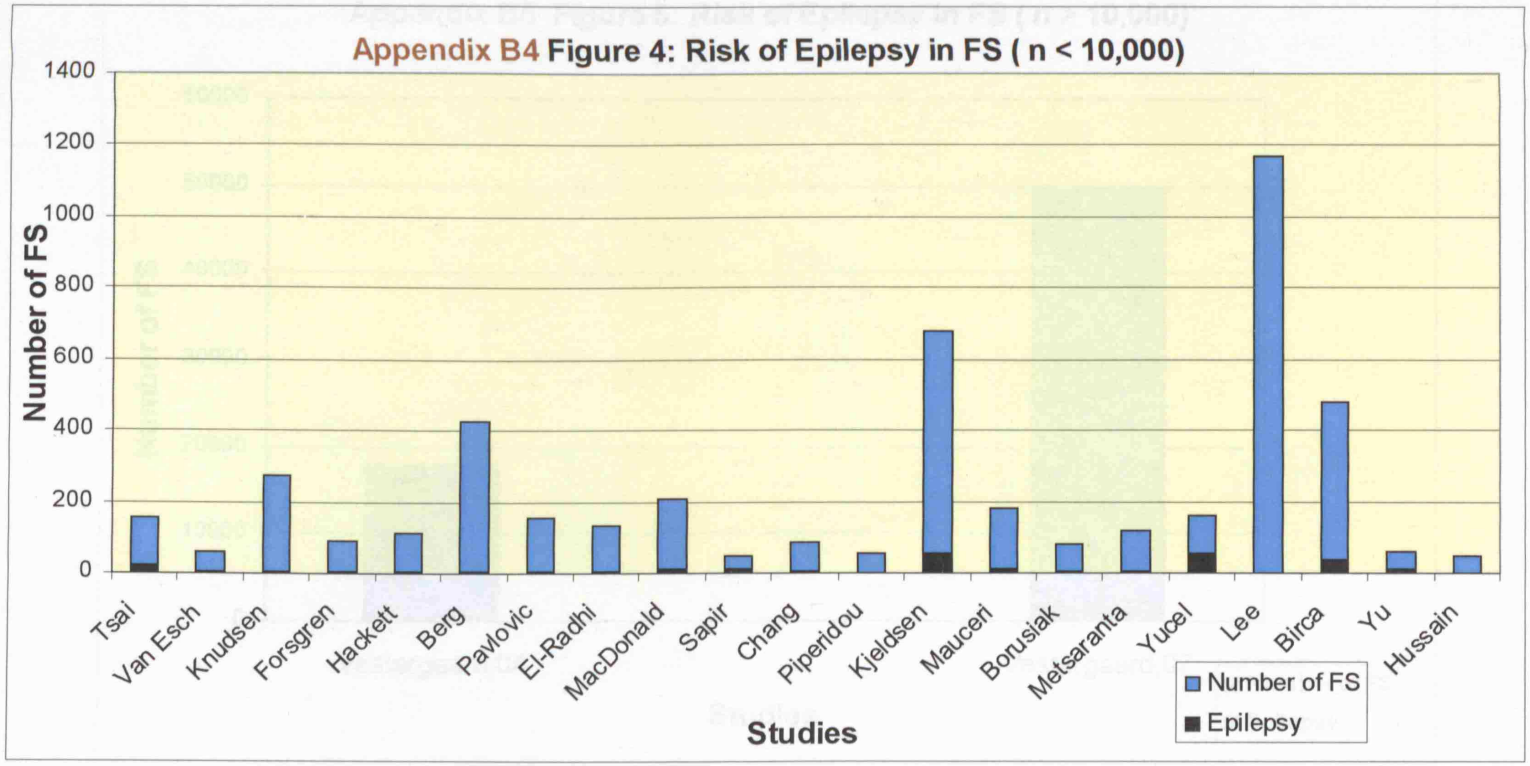
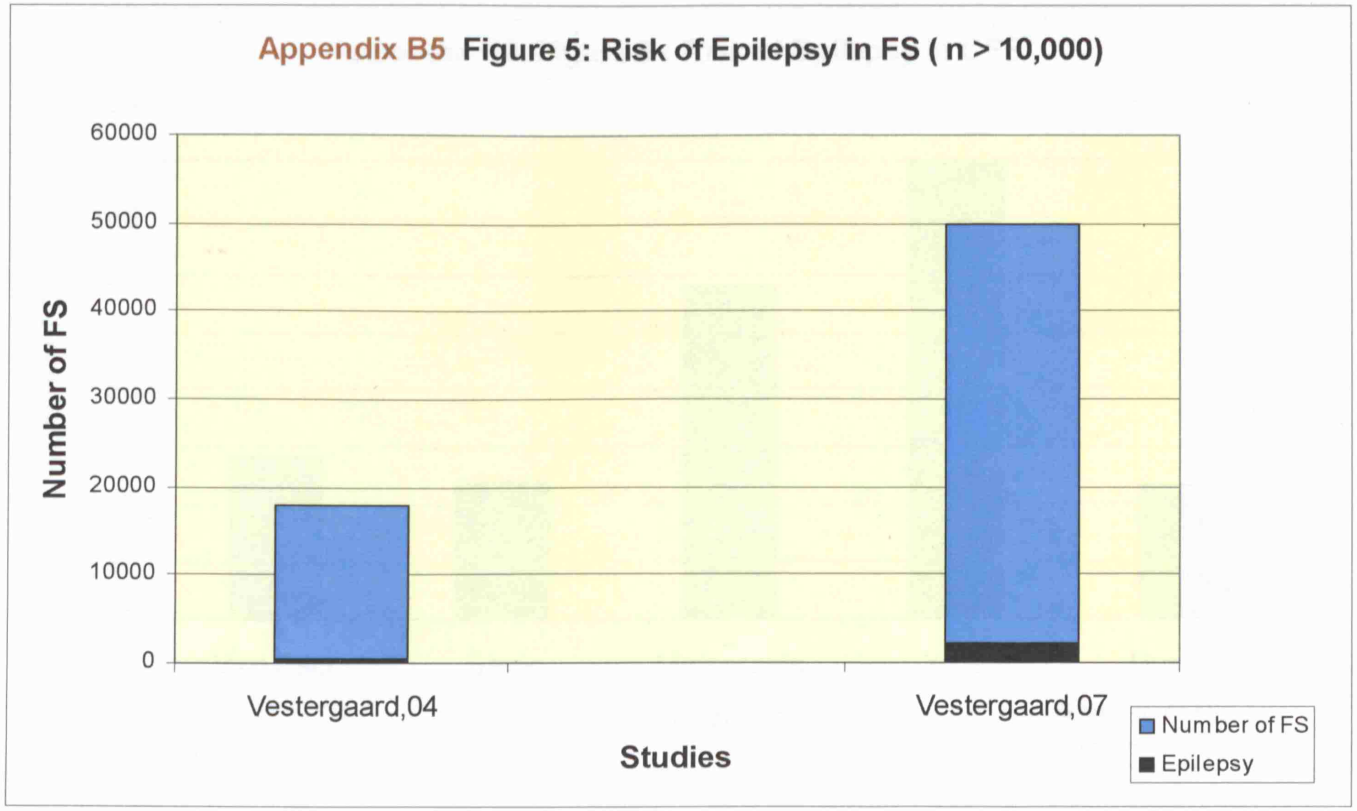
Takanashi
Hussain
Nishiyama
Studies
Number of FSE
Number of deaths

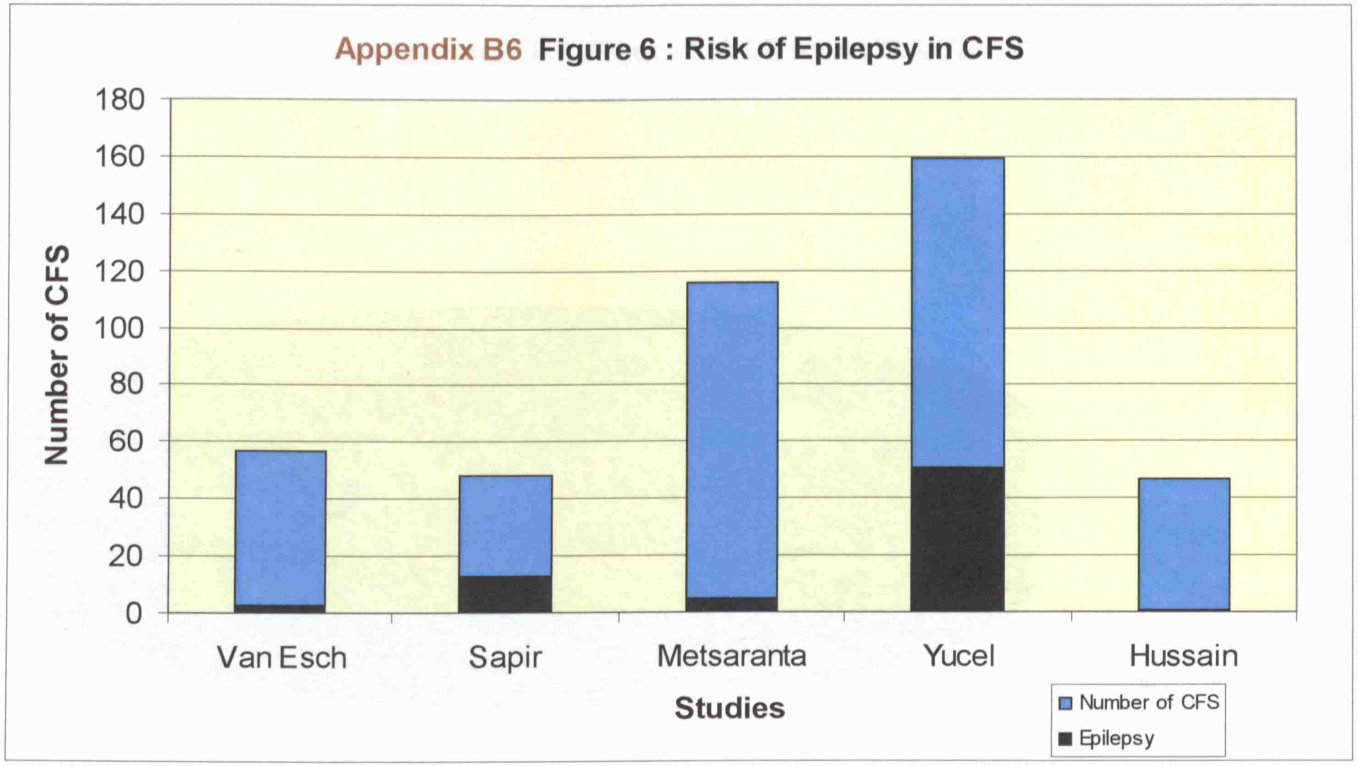

Appendix B3 Figure 3: Risk of Afebrile seizure in FS
Number of FS
1400
1200
1000
800
600
400
200
0
Verity
Rosman
Pavone
Laditan
Nevo
Miyake
Forsgren
Tarkka,98
Berg
Pavlovic
El-Radhi
Webb
Piperidou
Tarkka,03
Okumara
Lee
Studies
Number of FS
Number of afebrile seizure


Appendix B4 Figure 4: Risk of Epilepsy in FS (n < 10,000)
Number of FS
1400
1200
1000
800
600
400
200
0
Tsai
Van Esch
Knudsen
Forsgren
Hackett
Berg
Pavlovic
El-Radhi
MacDonald
Sapir
Chang
Piperidou
Kjeldsen
Mauceri
Borusiak
Metsaranta
Yucel
Lee
Birca
Yu
Hussain
Studies
Number of FS
Epilepsy

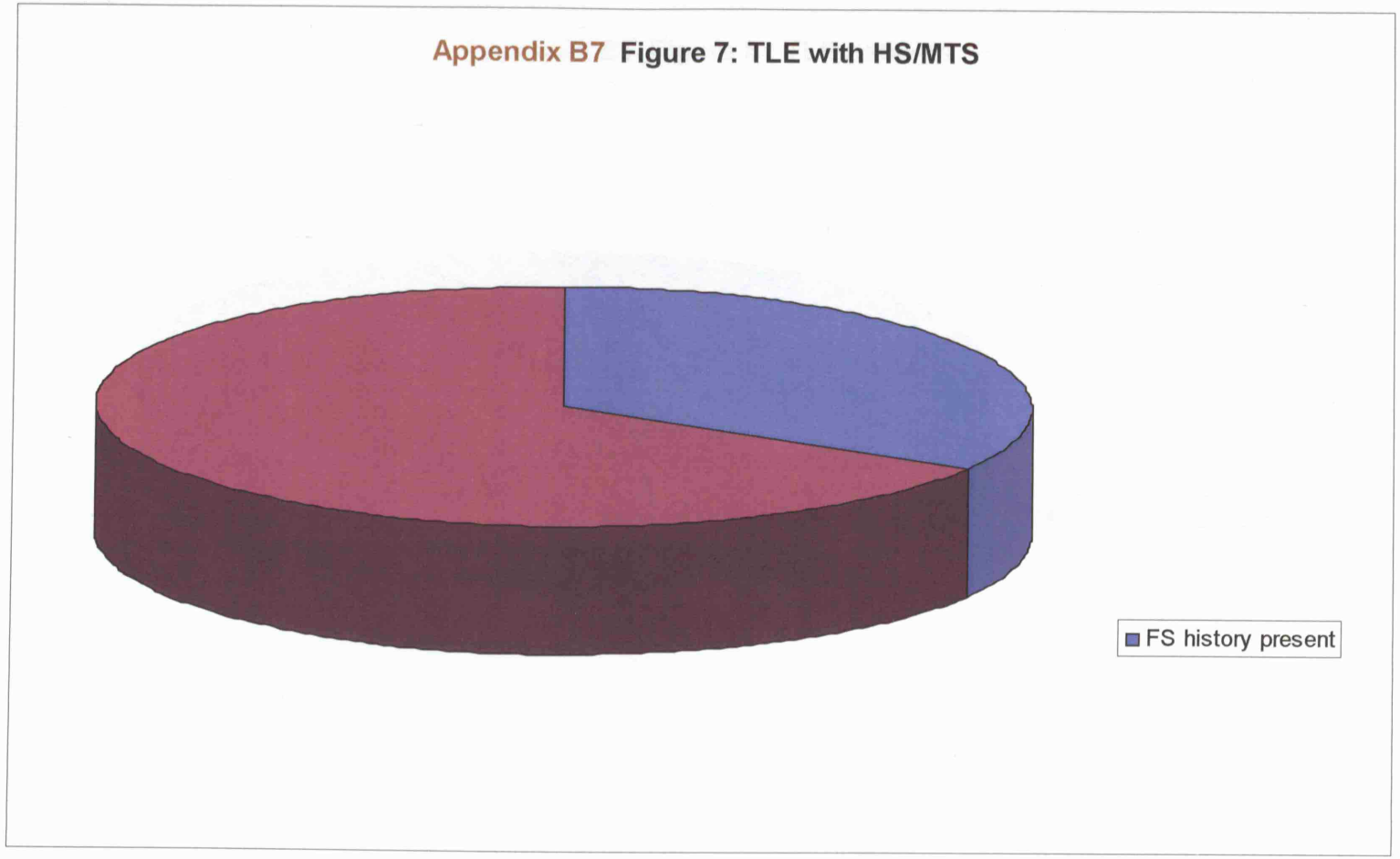
Appendix B5 Figure 5: Risk of Epilepsy in FS (n > 10,000)



Appendix B6 Figure 6 : Risk of Epilepsy in CFS



Appendix B7 Figure 7: TLE with HS/MTS



Appendix B8 Figure 8 : TLE patients